



# SURGERY

A Monthly Journal Devoted to the Art  
and Science of Surgery

## Editors

ALTON OCHSNER  
New Orleans

OWEN H. WANGENSTEEN  
Minneapolis

## Associate Editor

ALFRED BLALOCK  
Baltimore

## Advisory Council

DONALD C. BALFOUR, Rochester, Minn.

VILRAY P. BLAIR, St. Louis

BARNET BROOKS, Nashville

ELLIOTT C. CUTLER, Boston

WILLIAM E. GALLIE, Toronto

EVARTS A. GRAHAM, St. Louis

HOWARD C. NAFTZIGER, San Francisco

HARVEY B. STONE, Baltimore

ALLEN O. WHIPPLE, New York

## Editorial Board

FREDERICK A. COLLIER, Ann Arbor

EDWARD D. CHURCHILL, Boston

VERNON C. DAVID, Chicago

LESTER R. DRAGSTEDT, Chicago

RALPH K. GHORNLEY, Rochester, Minn.

ROSCOE R. GRAHAM, Toronto

SAMUEL C. HARVEY, New Haven

FRANK HINMAN, San Francisco

EMILE F. HOLMAN, San Francisco

EDWIN P. LEHMAN, University, Va.

FRANK L. MELENEY, New York

JOHN J. MORTON, Rochester, N. Y.

THOMAS G. ORR, Kansas City, Kan.

GEORGE T. PACK, New York

WILDER G. PENFIELD, Montreal

ISIDOR S. RAYDIN, Philadelphia

WILLIAM F. RIENHOFF, Jr., Baltimore

---

VOLUME 16

JULY—DECEMBER, 1944

---

ST. LOUIS

THE C. V. MOSBY COMPANY

1944



COPYRIGHT, 1944, BY THE C. V. MOSBY COMPANY

*(All rights reserved)*

Printed in the  
United States of America

*Press of*  
*The C. V. Mosby Company*  
*St. Louis*

# SURGERY

Vol. 16

JULY, 1944

No. 1

## Original Communications

### *Symposium on Endocrinology of Neoplastic Diseases*

#### SYMPOSIUM ON ENDOCRINOLOGY OF NEOPLASTIC DISEASES

##### INTRODUCTION

GRAY H. TWOMBLY, M.D., AND GEORGE T. PACK, M.D., NEW YORK, N. Y.

FOR THE individual who is as unfamiliar with the field of endocrinology as the average surgeon is apt to be, the relationship of hormones to cancer is a confusing one. Just the names of the preparations one reads in the current medical journals are apt to give one a hopeless feeling by their multiplicity and mixed etymologies.

Articles appear from time to time describing the production of cancer in experimental animals with hormones, observations which are disturbing to the doctor who wants to use them for his patient. Is he apt to produce a cancer if he treats the oophorectomized woman for her subsequent hot flashes?

Occasionally he is asked to see a patient suffering from a strange set of symptoms which are inexplicable until they are seen to fall into a reasonable pattern which, considered as the effects of too much of one of the hormones, is the result of a functional tumor of one of the endocrine glands. Such tumors are apt to be very rare and most of us are, in consequence, considerably puzzled when we meet with a patient who harbors one.

Recently, with the work of Huggins and co-workers<sup>1</sup> on carcinoma of the prostate, the indication for treating cancer with hormones has become an interesting possibility. The surgeon who has done his best to remove a cancer of the breast by radical mastectomy and then finds himself confronted a few years later with the distressing spectacle of multiple painful bone metastases cannot help but wish that hormone injections could be given which would bring the almost miraculous relief

that is seen in metastatic cancer of the prostate treated by castration or with diethylstilbestrol.

In an attempt to bring together the answers to these questions of what hormones there are, which ones produce cancer in animals and whether they produce cancer in men and women too, what rare symptom complexes are due to functional tumors of the endocrine glands, and whether cancer can be ameliorated or cured by hormones, we have collected the articles in the subsequent symposium. Perhaps the best form of introduction is to present in as simple a form as possible the scientific names of the hormones which have been isolated and characterized in the laboratory, and to indicate in a table the many trade names for the commercial preparations available. (Table I.)

The pituitary gland, the conductor of the glandular orchestra, produces many hormones, all of which as far as we know are proteins. They affect and control the thyroid (thyrotropic hormone), the gonads (gonadotropic hormones), the adrenals (adrenotropic hormones) the pancreas (diabetogenic hormone), growth (growth hormone), lactation (lactogenic hormones), water balance (intermedin), blood pressure and smooth muscle activity (vasopressin), and uterine motility (oxytocin). Two of the anterior pituitary hormones have been obtained in pure form,<sup>2</sup> and the last two, oxytocin and vasopressin from the posterior pituitary, can be separated completely from the anterior pituitary hormone. None of the pituitary hormones has been shown to be important in the etiology of cancer except secondarily (that is, cancer of the breast will not develop in a mouse hypophysectomized in infancy because it has little or no breast tissue).<sup>3</sup> The absence of these hormones seems to slow up the growth of cancer but does not prevent it altogether.<sup>4</sup> The injection of these substances seems to have no effect on the formation or growth of cancer.<sup>5</sup> Perhaps this may be partly due to the formation of antibodies or antihormones<sup>6</sup> when they are injected for they are commonly prepared from the glands of animals other than the species being tested. For instance, sheep and cattle are the source of most of the commercial preparations while rats, mice, and men are the animals bearing cancers which might be used to test their effects. Tumors of the pituitary give weird clinical pictures such as gigantism and acromegaly when the tumor is made up of cells producing growth hormone, Cushing's disease when the cells produce gonadotropic hormone, or infantilism or Simmonds' disease when the tumor presses upon and causes atrophy of these cells. The hormones of the pituitary, then, so far as we know now do not cause or control any form of cancer but may be useful by their effects in diagnosing tumors of that gland.

The same may be said for the thyroid and the adrenal glands. However, both of these organs produce substances which have been isolated in pure form. Thyroxin appears to be the active principle in thyro

globulin and from the adrenal three steroids, corticosterone, 17-hydroxycorticosterone, and desoxycorticosterone, as well as epinephrine from the adrenal medulla, have been isolated. None of these substances has been implicated as yet, either in the formation or treatment of cancer. Hyperthyroidism may result from metastases from a functional tumor of the thyroid.<sup>7</sup> Tumors of the adrenal are apt to give a Cushing syndrome and to produce large quantities of 17-ketosteroids in the urine. The suggestion has been made that this 17-ketosteroid excretion is changed in cancer patients, but just how and why is still under investigation.<sup>8</sup>

The hormones about which the most is known as to both chemical structure and carcinogenicity are those of the ovary and testis. The ovary produces two principal steroids, known as estradiol and progesterone. Estradiol, the structure of which is well established, is broken up and excreted in the urine as organic salts of estrone and estriol. Estradiol has been under suspicion for the last few years as a possible carcinogen because its injection into laboratory animals is followed by the formation of various kinds of carcinoma. In male mice it appears to produce carcinoma of the breast in susceptible strains.<sup>9</sup> It produces Leydig cell tumors of the testis in males of the Strong A strain.<sup>10</sup> It produces a cancer of the cervix in mice,<sup>11</sup> a tumor which does not occur in this species spontaneously. In guinea pigs it causes the formation of fibroma-like nodules on the uterus and in the walls of the gastrointestinal tract.<sup>12</sup> Gardner and his associates<sup>13</sup> have proved recently in rather conclusive fashion that the incidence of lymphosarcoma in mice injected with this material is definitely increased.

The meaning of these observations is obscure. It is probable that in male mice the appearance of cancer of the breast after the injection of large quantities of estrogens for a long time is the expression only of the development of considerable amounts of breast tissue by the hormone in animals bearing a more proximate etiologic factor, a virus found in the milk of susceptible mothers. When no breast tissue is present no cancer can develop. If breast tissue is produced with estrogens, susceptible animals can grow cancer in the tissue so developed.<sup>14</sup> That estrogens are not of themselves carcinogenic but rather that cancer develops secondarily in stimulated tissues is suggested by the fact that the synthetic estrogens seem to work as well as the natural steroids although their chemical structure is entirely dissimilar. The cancer-producing effect is not one that can be reproduced in all species, as evidenced by the failure of estrogenic treatment of guinea pigs and monkeys<sup>15</sup> to cause cancer.

Can estrogens cause cancer in women? Several authors think they have detected such a relationship<sup>16-18</sup> but the cases are rare and isolated and the evidence circumstantial. In these days when few women can complain of menopausal symptoms without receiving large amounts of

TABLE I

ENDOCRINE GLAND	HORMONE	COMMERCIAL PREPARATIONS
Anterior pituitary	Growth	Growth complex or factor Phyone Antuitrin G *Phybentrone
	Gonadotropic	Polyansin Antuitrin gonadotropic Gynantrin Prephysin
	Thyrotropic	Thyrotropic factor
	Lactogenic	Prolactin
	Adrenotropic	Polyansin Antuitrin
	Water balance	Intermedin
Posterior pituitary	Oxytocic	Pitocin Oxytocin
	Pressor	Pitressin Vasopressin
Placenta	Chorionic gonadotropic	A. P. L. Anterior-pituitary-like hormone Antuitrin S *Follutein Anteron Entromone Gestasol *Korotron Pregnyl Pranturon *Synapoidin Antophysin
Probably placenta of the pregnant mare	Pregnant mare's serum —gonadotropin	*Gonadin *Gonadogen
Thyroid	Thyroxin	Thyroxin Thyroid, desiccated *Thyroid extract *Proloid (contains thyroglobulin) *Endothylin (thyroglobulin)
Adrenal medulla	Epinephrine	Epinephrine hydrochloride Adrenalin Suprarenin Supranephrin Epinine Adrin
Adrenal cortex	Desoxycorticosterone	*Cortate Percorten } Synthetic *Doca
	Corticosterone	*Adrenal cortex extract *Eschatin *Corticocorbate } Natural Cortin
	17-Hydroxycorticosterone (Compound E)	*Cortalex (None on the market)

TABLE I—CONT'D

ENDOCRINE GLAND	HORMONE	COMMERCIAL PREPARATIONS
Ovary (follicle)	Estradiol	*Dimenformon
		*Ovocycin
		*Progynon DH
		*Progynon B.
		*Di-ovocycin
	Estrone	*Estrinyl (Methyl-estradiol)
		*Premarin (sodium estrone sulphate)
	Estriol	*Theelin
		*Emmenin (estriol glycuronide)
	Mixtures of the above and related substances derived from urine	*Theclol
		*Amniotin
		*Oestrogenic hormones or substances
		Follacero
		Menformon
		Folestrin
*Estromone		
*Urestrin		
*Estrogens		
(Synthetic estrogens)		
Diethylstilbestrol	*Stilbestrol	
	*Diethylstilbestrol	
Hexestrol	*Estiobene	
	*Hexestrol	
	*Hexital	
Ovary (corpus luteum)	Progesterone	*Progestin
		Lipolutein
		Progesterone
		Progestone
		*Proluton
		*Lutoeylin
		*Progestoral
		*Pranone
		*Lutoeylol
		Pregneninolone (Anhydro hydroxy-progesterone) (Has same effect as progesterone but is effective by mouth)
	Testis	Testosterone
*Oreton-M		
*Perandren		
*Neohombreol		
*Metandren		
Pancreas	Insulin	Insulin
		Iletin
		Protamine zinc insulin
Parathyroids	Parathyroid	Parathormone
		Paroidin

\*These compounds have been advertised in the Journal of the American Medical Association, Surgery, Gynecology and Obstetrics, Endocrinology, or Journal of Clinical Endocrinology in the last six months.

estrogenic hormone from their doctors, it would seem that cancer of the breast would occur more frequently after such medication if the drugs were really carcinogenic in the human species. We must conclude then that while estrogens undoubtedly cause certain kinds of cancer in mice, the assumption that they may do so in man must be labeled "not proved" for the present.

Progesterone, the other ovarian hormone, has never been implicated in the production of cancer in men or animals, although some years ago one of us (G. H. T.) observed that animals which had received multiple injections of this material seemed to develop an unexpected number of sarcomas.

Estrogens are elaborated by granulosa cell tumors of the ovary so that their effects, such as premature puberty and menstruation, or post-menopausal bleeding, may betray the presence of the parent tumors.

Estrogens are of particular interest at present because of the marked effects they may have on carcinoma of the prostate. It is really astonishing to see a patient suffering unbearable prolonged pain from metastatic prostatic cancer in bone lose all his pain, regain his appetite, and increase ten or fifteen pounds in weight under the influence of these drugs.<sup>19</sup> Unfortunately the effect is not always prolonged, as in one-third to one-half of the cases it wears off in eight to ten months.

Little can be said of the relationship of testosterone and cancer save that it occasionally causes premature puberty and virility and the infant Hercules type of child when elaborated in excessive quantities by a functional interstitial or Leydig cell type of tumor.<sup>20</sup> The same tumor in an adult causes no noticeable bodily change. Testosterone, by its lack following orchiectomy, is thought to influence the growth of cancer of the prostate. Its administration to patients who have cancer of the breast with bone metastases seems to cause a more rapid absorption of calcium and a consequent rapid growth of tumor,<sup>21</sup> although it does seem to relieve pain perhaps by raising the blood calcium level.

These, then, are the principal hormones elaborated by the body. Their etiologic relationship to cancer is obscure and has been demonstrated only in laboratory animals. While we have no proof that any such connection exists in man between hormones and the formation of cancer, the possibility that such could be the case rests so strongly in the mind that one finds oneself prescribing estrogenic therapy less and less frequently and then only in cases where there is clear indication for its use and preferably in those cases where this use can be controlled in amount and the patient followed and examined from time to time for the possible presence of cancer in the breast or uterus.

It is surprising how many women seem to get along just as well with mild sedatives and suggestion as with potent and possibly cancer-producing hormones.

#### REFERENCES

1. Huggins, C., Stevens, R. E., and Hodges, C. V.: Studies on Prostatic Cancer. II. The Effects of Castration on Advanced Carcinoma of the Prostate Gland, *Arch. Surg.* 43: 209-223, 1941.
2. Li, C. H., and Evans, H. M.: The Isolation of Pituitary Growth Hormones, *Science* 99: 182-184, 1944.
3. Gardner, W. U.: Persistence and Growth of Spontaneous Mammary Tumors and Hyperplastic Nodules in Hypophysectomized Mice, *Cancer Research* 2: 476-488, 1942.

1. Ball, H. A., and Samuels, L. T.: The Relation of the Hypophysis to the Growth of Malignant Tumors, *Am. J. Cancer* 26: 547-551, 1936; 32: 50-56, 1938.
5. Sugiura, K., and Benedict, S. R.: The Influence of Hormones on the Growth of Carcinoma, Sarcoma, and Melanoma in Animals, *Am. J. Cancer* 18: 583-602, 1933.
6. Twombly, G. H.: Studies of the Nature of Antigonadotropic Substance, *Endocrinology* 20: 311-317, 1936.
7. Piantz, V. K., Ball, R. P., Keston, A. S., and Palmer, W. W.: Thyroid Carcinoma With Metastases: Studied With Radioactive Iodine, *Ann. Surg.* 119: 668-689, 1914.
8. Rhoads, C. P., Dobriner, K., Gordon, L., Pieser, L. P., and Lieberman, S.: Metabolic Studies on the Urinary Excretion of Steroids in Normals, in Patients With Adrenal Hyperplasia, and in Cancer Patients, *Tr. A. Am. Physicians* 57: 203-208, 1942.
9. Laccasagne, A.: Relationship of Hormones and Mammary Adenocarcinoma in the Mouse, *Am. J. Cancer* 37: 414-424, 1939.
10. a. Bonser, G. M., and Robson, J. M.: The Effects of Prolonged Estrogen Administration Upon Male Mice of Various Strains: Development of Testicular Tumors in the Strong A Strain, *J. Path. & Bact.* 51: 9-22, 1910.  
 b. Hooker, C. W., Gardner, W. U., and Pfeiffer, C. O.: Testicular Tumors in Mice Receiving Estrogens, *J. A. M. A.* 115: 443-445, 1940.
11. Gardner, W. U., Allen, L., Smith, G. M., and Strong, L. C.: Carcinoma of the Cervix of Mice Receiving Estrogens, *J. A. M. A.* 110: 1182-1183, 1938.
12. Lipschutz, A., and Vargas, L., Jr.: Structure and Origin of Uterine and Extragenital Fibroids Induced Experimentally in the Guinea Pig by Prolonged Administration of Estrogens, *Cancer Research* 1: 236-249, 1941.
13. Gardner, W. U., Dougherty, T. P., and Williams, W. L.: Lymphoid Tumors in Mice Receiving Steroid Hormones, *Cancer Research* 4: 73-87, 1944.
14. Twombly, G. H.: Breast Cancer Produced in Male Mice of the C 57 (Black) Strain of Little, *Proc. Soc. Exper. Biol. & Med.* 41: 617-618, 1940.
15. Engle, E. T., Krakower, C., and Haagenen, C. D.: Estrogen Administration to Aged Female Monkeys With no Resultant Tumors, *Cancer Research* 3: 858-866, 1943.
16. Auchincloss, H., and Haagenen, C. D.: Cancer of the Breast Possibly Induced by Estrogenic Substances, *J. A. M. A.* 114: 1517-1523, 1940.
17. Allaben, G. R., and Owen, G. E.: Adenocarcinoma of the Breast Coincidental With Strenuous Endocrine Therapy, *J. A. M. A.* 112: 1933-1934, 1939.
18. Parsons, W. W., and McCall, E. F.: The Role of Estrogenic Substances in the Production of Malignant Mammary Lesions, With Report of Case of Adenocarcinoma of the Breast, Possibly Induced by Strenuous Estrogen Therapy, *SURGERY* 9: 780-786, 1941.
19. Dean, A. L., Woodard, H. Q., and Twombly, G. H.: The Endocrine Treatment of Cancers of the Prostate, *J. Urol.* 49: 108-117, 1943.
20. Warren, S., and Olehausen, K. W.: Interstitial Cell Growths of the Testicle, *Am. J. Path.* 19: 307-331, 1943.
21. Fariow, J. H., and Woodard, H. Q.: The Influence of Androgenic and Estrogenic Substances on the Serum Calcium, *J. A. M. A.* 118: 339-343, 1942.



# TUMORS IN EXPERIMENTAL ANIMALS RECEIVING STEROID HORMONES

W. U. GARDNER, PH.D.,\* NEW HAVEN, CONN.

*(From the Department of Anatomy, Yale University School of Medicine)*

A CARCINOGEN might be defined as any substance or agent, chemical or physical, which when applied under certain conditions is followed by the appearance of tumors which would not have appeared otherwise. Estrogens would be carcinogenic if classified according to this definition. Perhaps they should be so classified—or perhaps the definition should be so modified as not to include the estrogenic chemicals presumably capable of origin within the body. It shall be the purpose of the present review to summarize a portion of the experimental studies on the relation of estrogens to carcinogenesis.<sup>1</sup>

## GENERAL OBSERVATIONS

Estrogens were first determined biologically by their capacity to induce growth and cornification of the vaginal mucosa of rats and mice.<sup>2</sup> The other genital tissues of ovariectomized females also showed hyperplasia and hypertrophy following the injection of estrogens<sup>3</sup> which might be characterized superficially as growth-stimulants of specific tissues.<sup>4</sup> In the absence of estrogens or of the ovaries, which are associated with their elaboration, the genital tissues remain infantile or become atrophic. The nature of the process whereby estrogens affect the hypertrophy of the genital tissues is unknown. The absence of trophic manifestations of estrogens on in vitro preparations of genital tissues indicates a lack of direct action on the tissue cells. Vaginal or uterine tissues grown in culture in the presence of estrogen showed no evidence of stimulation.<sup>5</sup> The trophic stimulation in the genital tissues may be elicited by vascular changes in these organs.<sup>6</sup> Their stimulation of all genital tissues except the mammary glands in hypophysectomized animals indicates an independence from the growth-stimulating properties of the hypophysis. Although many attempts have been made to determine how genital growth is affected by estrogens, it can be said with any certainty only that "this is what happened when the animal was subjected to this treatment."

The growth-stimulating activity of ovarian hormones was probably responsible for their original association with the initiation of cancer. Mammary cancer in mice is sex-limited; under normal circumstances males are not affected.<sup>7, 8</sup> Ovariectomy at early ages decreased, and

Received for publication, Oct. 2, 1943.

\*The investigations undertaken by the writer and mentioned in this review have been supported by The Anna Fuller Fund and The Jane Coffin Childs Memorial Fund for Medical Research.

reproductive activity increased, the incidence of mammary tumors in mice of certain inbred lines but not of other lines.<sup>8-11</sup> Subsequently, strains of mice were developed which showed, within each strain, consistent, but among the different strains, varying incidences of mammary tumors.<sup>12, 13</sup> Leo Loeb probably first expressed the influence of hormonal factors in cancer in experimental animals by the formula: Genetic or inherited factors plus internal secretions give mammary cancer.

An almost universal characteristic of female reproductive phenomena is its cyclic or rhythmic nature. Periods of proliferation and hypertrophy alternate with periods of atrophy or regression during the different phases of the estrous or menstrual cycles. This generalization might afford a mechanism protecting against too great or prolonged trophic stimulation. The genital tissues were at least capable of responding when periodically stimulated. Under experimental conditions could the stimulation be more or less indefinitely prolonged? What would be the character of the response under such conditions? Finally, would any relation exist between an accentuated or prolonged trophic stimulation of specific tissues and the assumption of the quality of unrestricted or malignant growth by these tissues? Attempts to obtain answers to these questions undoubtedly prompted the experiments to be summarized.

Investigations in which mice have been used have contributed most extensively to the knowledge of hormonal factors in carcinogenesis. Geneticists observed many years ago that certain inbred lines or groups of mice showed a high incidence of spontaneous mammary adenocarcinoma in females. Further inbreeding and selection has resulted in the existence of several inbred strains in which mammary tumors have appeared for many successive generations.<sup>13</sup> Among mice of other equally or nearly equally inbred strains, mammary tumors appear with less frequency, and in still others they rarely occur. It is but natural that such well-controlled material should be used in a study of factors influencing the incidence of cancer.

*Ovariectomy and Mammary Cancer.*—The ovaries have been associated with the development of the mammary glands for many years.<sup>14</sup> The possible relation of these glands to mammary cancer was investigated by their removal or by their transplantation into males of the same strain.<sup>11</sup> Ovariectomy of mice at ages of 3 to 5 months largely inhibited the occurrence of mammary tumors. The incidence of such tumors was greater in mice ovariectomized when 5 to 7 months old and was not altered in mice ovariectomized at later ages.<sup>7</sup> These observations have been confirmed in their essential points by other investigators,<sup>10, 11</sup> although the ages at which tumors did not appear subsequent to castration varied.

An exception to the usual observation that ovariectomy at an early age prevents the appearance of mammary tumors in mice has recently

been reported, but it need not alter the inference that the removal or reduction of ovarian hormones reduces the incidence of mammary cancer. Mice from two strains, ovariectomized while very young, developed mammary tumors many months later.<sup>15</sup> These mice showed either a marked hypertrophy or tumors of the adrenal glands, and their accessory genital organs showed evidence of estrogenic stimulation. Similar observations were made on hybrid mice ovariectomized when about 2 months old.<sup>16</sup> Male mice, which normally are not subject to mammary tumors, showed such lesions when they were castrated at a very early age.<sup>15d</sup> It might be concluded that the disturbance of the endocrine system created by a gonadal deficiency results in the alteration of adrenal function and morphology and frequently the acquisition of adrenal adenomas or even carcinomas. These altered adrenal glands compensate in part for the removed ovaries, the mammary glands are stimulated, and mammary tumors appear. In my opinion these experiments are uniquely significant in that they demonstrate the nice balance which must exist in the normal animal and how prolonged alteration of this balance may slowly alter other functions materializing in profound changes which may in some ways even overcompensate for the initial deficiency. Similar adrenal lesions have been described in castrated guinea pigs, although in this species the hosts were masculinized.<sup>17</sup>

*Ovarian Grafts and Mammary Tumors.*—The second surgical approach to the problem of ovarian hormones in mammary carcinogenesis has likewise given equivocal results. The transplantation of ovaries into male mice of the same strain led to the appearance of mammary tumors in some of the recipients.<sup>11, 18</sup> The incidence of such tumors was not high but approached that of virgin females of the same strain.<sup>11</sup> Male mice of other strains in which the females are susceptible to mammary tumors did not acquire mammary tumors after ovaries had been grafted into them.<sup>19, 20</sup> The grafting of a female animal to a male (parabiosis) did not result in mammary tumors in the male.<sup>21</sup> The later experiments create a more complicated endocrine relationship than the transplantation of ovaries. Mice which had ovarian tumors subsequent to x-irradiation showed a much higher incidence of mammary tumors than mice in which ovarian neoplasia did not occur.<sup>22</sup>

*Other Methods of Investigation of Ovarian-Mammary Tumor Problem.*—Two more or less direct methods of experimentation were afforded at this point to investigate how the ovary or its hormones might be related to mammary carcinogenesis. In the first place the possibility of an excessive production of ovarian hormones in mice of the tumor-susceptible strains or lines could be investigated. In the second place additional or excessive amounts of hormones could be added to mice of the different strains and the incidence of tumors observed.

*Studies on Estrogen Levels in Mice of Strains Which Differ in Susceptibility to Mammary Cancer.*—The hormonal environment to which mammalian tissues are exposed might be estimated to some extent by study-

ing the comparative reproductive capacities of animals of tumor-susceptible or resistant groups, by comparing the mammary glands, or vaginal estrous cycles. Direct estimation of the elimination of sex hormones in animals of different strains can also be made.

In some instances it has been possible to associate evidence of excessively prolonged or frequent estrous periods with the tendency to develop mammary tumors.<sup>23</sup> When the previously stated observations were extended to include mice of several strains, the correlation no longer existed.<sup>24</sup> Mice of different strains had estrous cycles which tended to differ from each other in the length and frequency of estrus, but this was not necessarily related to the tendency to acquire mammary tumors.<sup>25</sup> No differences were detected in the estrous rhythm, age of onset, or age of cessation of estrus of other low- and high-tumor strains.<sup>26</sup>

The mammary glands might also afford some indication of the hormonal environment. Several investigators have noted differences in the mammary glands which they associated with the tendency for certain strains to acquire mammary cancer.<sup>27</sup> These differences in morphology involved essentially the presence of localized areas of alveolar tissue described by Haaland.<sup>28</sup> When the glands of young<sup>29</sup> or old mice<sup>30</sup> of ten and six strains, respectively, were compared, the differences in general mammary morphology could not be associated with the tendency to acquire tumors. Strain differences did exist, however.<sup>29</sup> The morphologic aspects that could be associated with the tendency to acquire mammary tumors involved the specific proliferation of localized nodules of mammary tissue in otherwise atrophic glands. "The presence of localized proliferation of mammary tissue in animals from strains susceptible to mammary cancer, while the rest of the gland was in a state of regression or inactivity, indicates that various areas of the gland show different growth responses in the presence of a supposedly uniform environment. The importance of localized nodular areas in otherwise involuted glands is indicated by their frequent occurrence in strains liable to progressive adenomatous and malignant change. The early appearance of hyperplastic nodules, their numbers, and their variable structure suggest a progressive series of abnormal changes in the mammary parenchyma leading to malignancy."<sup>30</sup> The extent of involution or proliferation of the internodular areas was not related to mammary tumor susceptibility. Recently one group of investigators who observed a greater abundance of alveolar elements in the glands of a high- (dba) than in a low-tumor strain of mice noted that the tendency was transmitted by the female in hybridization.<sup>31</sup> "There is a strong positive correlation between the architecture of the mammary glands in different types of mice with regard to the degree of its disposition for cancer." Other morphologic features of the mammary glands were of intermediate prominence in the hybrids irrespective of the maternal parent. Similar observations have been made in another laboratory when the mammary

glands of mice of the dba strain were compared with mice of the C<sub>57</sub> strain.<sup>32</sup> Experiments involving reciprocal hybridization of other high- and low-tumor strains failed to reveal significant differences in the general mammary morphology, although the localized hyperplastic nodules were largely transmitted by the female parent.<sup>33</sup> The observations on the comparative morphology of the mammary glands of mice of strains showing different susceptibilities to spontaneous mammary tumors are not in agreement. The writer's observations indicate no relation of general mammary structure to tumor susceptibility as contrasted to the observations of two other investigators.

Reproductive histories have been recorded for mice of several inbred strains presumably maintained under rather uniform conditions.<sup>34</sup> Striking strain differences have not been revealed which could be associated with the tendency to acquire cancer. In some strains virgin female mice frequently acquire mammary tumors<sup>35</sup> and frequent pregnancies may increase the incidence in mice of low-tumor strains.<sup>36</sup>

Recently studies have been conducted on the urinary elimination of estrogenic substances from mice of the high- and low-tumor strains<sup>37</sup> and also of the capacity of hepatic tissues of these mice to inactivate estradiol.<sup>38</sup> These studies have not revealed significant differences that could be associated with susceptibility to mammary cancer.

Mice of several inbred strains showed some variation in their response to minimal amounts of estrogen. One investigator attached little significance to the slightly greater response of the low-tumor CBA mice than of the high-tumor A mice.<sup>36</sup> Another group compared the vaginal response of C<sub>57</sub> and dba mice and found that the latter required nearly three times as much hormone as the low-tumor mice and that F<sub>1</sub> hybrids needed intermediate amounts,<sup>39</sup> but resembled the low-tumor C<sub>57</sub> strain more closely than the dba strain. The females which had genital organs least susceptible to estrogens were considered to produce the largest amounts of hormone under normal conditions. The ovaries of mice of the dba strain were larger than those of C<sub>57</sub> mice.<sup>32</sup> The mice of one inbred strain (CBA) showed less uniformity of response of the vaginal epithelium to estrogens than market mice of variable origin.<sup>40</sup>

These observations might be summarized as follows: (1) The strain-limited tendency of mice to acquire mammary tumors cannot be associated consistently with evidences of an abnormal intrinsic hormonal environment. (2) The mammary glands of susceptible mice may or may not be identified from those of low-tumor strains by their general morphologic characteristics but they do show localized areas of hyperplastic epithelial tissues rarely found in the glands of mice of low-tumor strains. The latter condition can be associated with the tendency for mammary tumors to appear and, as will be discussed later, may represent early stages in the assumption of malignancy.

Rats and rabbits of some strains or groups acquire benign or malignant mammary or uterine tumors. These tumors appear among animals

showing evidences of an altered reproductive capacity or presenting a glandular syndrome. The benign mammary tumors in rats of the Albany strain occur in animals showing a high incidence of sterility, irregularities of estrous cycles, and a tendency to have hypophyseal adenomas.<sup>41</sup>

The mammary<sup>42</sup> and uterine tumors<sup>43</sup> in rabbits occurred in animals which at some time had toxemia of pregnancy<sup>44</sup> and had acquired a persistent hepatic damage. Associated with this condition were degenerative lesions in the adrenal cortices and hypophyseal hypertrophy.<sup>42</sup> The genital tissues showed prolonged periods of general hyperplasia, progressing to benign neoplasia and finally malignant tumors.

Studies of these types are of great interest. In some ways they contribute much more than experiments in which one or more sex hormones are administered. Such observations must be made in many animals so that the possibility of their etiologic relationship or concomitant nature can be evaluated. The rats and rabbits mentioned are representatives of selected populations.

*Experimental Alteration of Estrous Cycles.*—The endocrine system may be profoundly disturbed by experimental manipulation. The removal of the greater part of the ovaries of guinea pigs has resulted in a disturbance of the gonad-hypophyseal relationship and excessive uterine hyperplasia in guinea pigs.<sup>45</sup> The partial destruction of the ovaries by x-irradiation also resulted in a cessation of the estrous cycles and evidence of excessive ovarian activity.<sup>46</sup> The ovaries of the guinea pigs were largely composed of interstitial tissue. The estrous cycles of rats<sup>47</sup> and mice<sup>48</sup> may be permanently altered if testes of littermates are grafted into them shortly after birth. The mice showed a marked hypertrophy of their genital tracts and prolonged periods of estrus. The reproductive activity of rats may be profoundly and permanently altered by brief treatment with estrogens or androgens before the fifteenth day after birth.<sup>49</sup> Some of the animals had uterine lesions similar to those attributed to chronic estrogenic treatment.<sup>49b</sup>

These experimentally produced "syndromes" probably all result from an altered endocrine balance which destroys the capacity for the rhythmic characteristics of female reproductive phenomena. The amount of estrogenic substance effective within the body is probably not excessive in amount but the tissues are stimulated continuously and are not permitted to regress.

*Administration of Estrogenic Hormones and Mammary Tumors.*—The earlier experiments on the administration of estrogens upon the appearance of mammary cancer in experimental animals did not reveal any detectable carcinogenic effect. Estrogenic preparations were not concentrated.<sup>10, 50</sup> Moderate or large amounts of hormone could not be administered over prolonged periods. A cystic and adenomatous condition of the mammary glands was observed which was compared with Reclus disease.<sup>50</sup>

Lacassagne, in 1932, first reported a carcinogenic effect of estrogens on the mammary glands. Multiparous female mice of one of his strains frequently showed mammary tumors. Male mice never acquired such tumors. The injection of folliculin benzoate in oily solution into male mice, starting shortly after their birth and continued at weekly intervals, resulted in mammary tumors. The tumors resembled those which appeared among the females. Mammary tumors thus appeared in animals in which they would not have appeared had estrogens not been administered.

These experiments might be interpreted in either of two ways: (1) Estrogens directly elicit abnormal or malignant growth, or (2) estrogens merely initiate mammary proliferation so that tissue is available to undergo malignant transformation.

Lacassagne<sup>51</sup> immediately set about checking these interpretations. Mice from one strain showing a low incidence of mammary tumors showed a higher incidence of such tumors after the injection of estrogens. Another strain of mice in which mammary tumors rarely appeared showed no tumors after the injection of estrogen.

Lacassagne's observations have been confirmed and extended by many investigators. Male mice from strains in which the females develop mammary cancers acquire such tumors after the injection of estrogens.<sup>52</sup> In some strains the tumors occur at earlier ages than in the untreated mice. The incidence of mammary tumors was not as high in estrogen-treated mice of some other high-tumor strains or hybrid groups as in multiparous females of the same strains.<sup>53</sup> Only in a very few instances have mammary tumors appeared among estrogen-treated inbred mice of low-tumor strains,<sup>54</sup> or stock mice<sup>55</sup> in higher incidences than among the multiparous controls. The incidence of tumors was not exceptionally high in these latter experiments.

The administration of estrogens of widely different chemical structures such as estrone, estradiol, equilin, equilenin,<sup>56</sup> and their benzoates or propionates, stilbestrol,<sup>57</sup> and triphenylethylene<sup>58</sup> affect similar mammary changes when administered in amounts that are physiologically comparable. This generalization is apparently true for both the capacity to elicit the normal proliferation of the mammary tissue<sup>59</sup> as well as any association with abnormal or malignant proliferation. The estrogenic hormones apparently do not have any chemical specificity for mammary carcinogenesis that cannot be associated with their estrus-producing capacity.

The estrus-producing hormones in mice act only in combination with factors or "influences" transmitted from parents or maternal parent to offspring for mammary carcinogenesis. The incidence of mammary tumors among mice from strains showing a high or moderate incidence of cancer is usually increased or tumors appear earlier in the estrogen-treated animals than in the respective controls. Mice from strains in

which spontaneous mammary tumors rarely appear do not acquire or rarely acquire such tumors when estrogens are administered. Hybrid male mice obtained by crossing mammary tumor-susceptible and low-mammary tumor strains, when treated with estrogens, have an incidence of cancer approaching that of the maternal strain.<sup>60</sup> A similar tendency for the appearance of cancer exists among untreated multiparous females of comparable origins.<sup>61</sup> The tendency to acquire mammary tumors was transmitted largely through the ingestion of milk during the nursing period.<sup>61</sup> Young mice born from tumor-susceptible mothers but fostered on low-tumor females did not acquire tumors after pellets of estrone or estradiol benzoate had been implanted.<sup>62</sup> The young of low-tumor mothers which were fostered on high-tumor females acquired mammary tumors when estrogens were administered in one experiment<sup>63</sup> but not in another.<sup>62</sup> These observations indicate that estrogens are no more than a contributing factor in the initiation of mammary neoplasia. Although in male mice the estrogens result in some development of the mammary glands, in the absence of which mammary tumors do not appear, other factors must also exist in these animals before tumors arise.

This conclusion is supported by the observation that mammary cancers appear in male mice from tumor-susceptible strains at six to sixteen months after the last injection of estrogen.<sup>64</sup> The period of treatment of such animals must be sufficiently prolonged to assure considerable mammary development (eight to twelve weeks).<sup>65</sup> The incidence of tumors in such animals is usually considerably lower than in mice continually treated with estrogen.

The amounts of estrogenic hormones injected have also been studied in relation to their mammary carcinogenic actions. Amounts large enough to result in optimal growth of the mammary ducts do not appear as effective in mammary carcinogenesis as larger amounts.<sup>66</sup> Very large amounts were not only quite toxic as far as the animals were concerned, but inhibited mammary proliferation and the incidence of mammary tumors was low.<sup>67</sup> Within limits, the larger the amount of estrogen administered the earlier mammary tumors appeared.<sup>68</sup>

*Mammary Tumors in Estrogen-Treated Animals of Other Species.*—Mammary lesions of several types have been observed in rats given estrogens. All of six castrated female rats which had received 30  $\mu$ g. of estrone daily for 331 days or more, showed multiple mammary cysts and one had an adenofibroma.<sup>69</sup> Mammary cancer appeared in other treated rats.<sup>70</sup> Other investigators observed cyst formation and stunted growth of the glands in animals similarly treated.<sup>71</sup>

A very high incidence of mammary tumors occurred among rats given pellets or both pellets and injections of estrogens.<sup>72</sup> In some groups most of the animals developed tumors. Among 555 rats treated with estrogens, 202 mammary cancers appeared.<sup>73</sup> Two animals showed



multiple metastases to the lungs and lymph nodes. The larger the dose of hormone the earlier the tumors appeared.<sup>72</sup> Untreated rats of the same colony did not develop mammary tumors.

Approximately 60 per cent of the rats which survived 7 months or more and which had pellets of estrone implanted on the fifth to seventh days of life acquired mammary tumors after 226 or more days. The tumors were usually multiple and grow slowly although they were extremely hyperplastic.<sup>74</sup>

Metastatic growth was found in the lungs of one rat bearing a mammary tumor.<sup>75</sup> These tumors failed to grow following transplantation into other animals or into other sites in the same animal unless the hosts had pellets of estrone implanted. The tumors regressed after removal of the estrogen and after the injection of progesterone.

*Experiments With Monkeys.*—The breasts of young male monkeys grew to morphologically complete tubulo-alveolar glands when estrogen was administered.<sup>76</sup> Prolonged periods of treatment with large amounts of estrogen resulted in "stunted" mammary glands.<sup>67</sup> Other observations on monkeys given even larger amounts of estrogen, likewise, failed to reveal malignant growth although metaplastic islands appeared in some glands.<sup>77</sup> Localized hyperplastic or secreting areas of mammary tissue were found in ovariectomized monkeys.<sup>78</sup>

*Other Species.*—Although large amounts of estrogens have been administered to animals of several species, especially rabbits and dogs, mammary tumors have not been reported.

*Mammary Changes Elicited in Animals Receiving Estrogens.*—It has been stated that the mammary glands of adult and old mice of the tumor-susceptible strains usually showed localized hyperplastic nodules.<sup>28, 30, 33</sup> These nodules varied greatly in structure from small lobules of alveoli, sometimes secreting, to small hyperplastic adenomas or even small adenocarcinomas histologically similar to the larger tumors.

Similar morphologic changes occurred in the glands of estrogen-treated male or female mice of the same strains.<sup>33, 79</sup> Some of the lesions have been compared with the microscopic appearance of nonmalignant hyperplastic lesions in man.<sup>32, 50, 51b, 52, 80</sup> In mice these localized hyperplastic lesions can be said to be precancerous in the sense that they have been so uniformly found in mice with the tendency to acquire mammary neoplasia. The tissues composing these nodules must respond to other stimuli, which elicit reactions in the normal mammary tissues. Many of these nodules are found in stages of regression indicating that many are not autonomous. Some of these nodules apparently go through several stages of atypical growth terminating in adenocarcinoma.<sup>79b</sup> Although mammary cancer may seem to be a local disease, the wide distribution of the "precancerous" lesions indicates that all of the mammary tissue or that many areas of mammary tissue may be involved simultaneously.

Another type of morphologic change occurring in the mammary glands of estrogen-treated mice is found both in the low- and high-tumor mice.<sup>72, 73, 79, 80</sup> The larger ducts and some of the smaller ducts and alveoli become distended with a concretion-like secretion. The ductal distention may be extreme. The epithelium of the surrounding ducts may be absent or epithelial cells may surround the secretion. A moderate increase in the surrounding fibrous connective tissue may occur. The effects of age and estrogen treatment on the mammary connective tissue have been studied extensively.<sup>72, 73, 79, 81</sup>

*Summary of Effects of Estrogens on Mammary Carcinogenesis.*—Several phases of the investigations just reviewed indicate that estrogens may have little direct effect upon mammary carcinogenesis in mice. These might be summarized briefly as follows: (1) The relative physiologic activity of the different estrogens is associated with the tendency for their injection to result in the appearance of tumors in suitable animals. (2) Hereditary or transmitted factors dominate the appearance of tumors in estrogen-treated animals. (3) In suitable animals mammary tumors can appear long after the last exposure to injected estrogens. (4) To these may be added the fact that in mice estrogens have very little mammary stimulating activity in the absence of the pituitary gland, as will be discussed later.

On the other hand some evidence indicates carcinogenic effect of estrogens: (1) Without mammary glands of at least moderate size which develop when estrogens are administered to intact mice, no mammary tumors appear. (2) Amounts of estrogen adequate for mammary proliferation are not necessarily optimal for mammary cancer.

The mechanism whereby mammary cancer appears when estrogens are injected in suitable animals is not known. It has been stated that "estrogenic hormones do not cause cancer formation because they give origin to a larger amount of tissue, which thus would be a more favorable field of attack for the unknown agent representing the real cause of the cancerous transformations. But the hormone leads to the formation of new tissue because it stimulates the glands and because it stimulates the gland tissue it causes the cancer formation. Both increase in the amount of tissue and cancerous transformation are therefore the result of the same condition, they are coordinated and not subordinated phenomena."<sup>78a</sup> This might represent one extreme viewpoint.

There is also sufficient experimental evidence to suggest the following theory. Mammary growth occurs in the animals with functional pituitary glands when estrogens are injected. In the presence of some other factor or agent and estrogen, localized proliferative or pre-cancerous nodules of breast tissue appear in glands in which other areas may be refractory to estrogens. The appearance of mammary adenocarcinoma in and among the localized nodules can occur subsequently in the absence of estrogens. Many of these nodules are re-

versible, attaining certain stages of atypical structure and regressing. If the active growth-stimulating phase were responsible for the tumors the neoplasia might be expected to occur early. Instead, cancer does not appear until the greater part of the glands have become refractory to estrogens. Estrogens may therefore contribute to the premalignant phases of tissue change or to the environment in which these changes occur.

*Factors Involved in Mammary Proliferation.*—A number of years ago it was considered that estrogens stimulated mammary growth but the absence of, or limited mammary growth in estrogen-treated hypophysectomized animals altered this interpretation.<sup>14</sup> Several theories have been proposed: (1) Estrogens may act upon the pituitary causing a release of a mammotropin.<sup>82</sup> (2) The mammary glands may be incapable of response to estrogen because of the other deficiencies existing in hypophysectomized animals.<sup>83</sup> When progesterone, desoxycorticosterone, or prolactin were administered with estrogen, mammary growth occurred.<sup>83a, b</sup> In intact animals the cutaneous application of small amounts of estrogen induced mammary growth only in the subjacent glands.<sup>83d, e</sup> During the latter part of pregnancy the hypophysis is not necessary for mammary growth.<sup>14</sup>

In intact animals of some species estrogen alone will result in complete mammary growth,<sup>76</sup> but in others progesterone is required for the development of the alveoli. When the corpora lutea are active, as during pregnancy or pseudopregnancy, alveoli form.<sup>85, 86</sup> Progesterone may induce some alveolar development when administered with estrogens.<sup>85</sup>

*Influence of Androgens and Other Steroid Hormones When Administered Alone or With Estrogens.* Mammary growth occurred in mice receiving several different steroid hormones such as testosterone, androsterone, progesterone, and desoxycorticosterone when they are administered in large amounts.<sup>87</sup> Two of three mice of a tumor-susceptible strain which received 100  $\mu$ g. of estrone and 0.5 to 1.0 m.g. of testosterone on alternate weeks developed mammary tumors after several months.<sup>88</sup> Also, two females of the same strain given testosterone (0.5 to 1.0 mg. weekly) from birth acquired mammary tumors. Similar results were obtained with larger numbers of mice and with other strains.<sup>89</sup>

Testosterone propionate, when administered in very large amounts to uniparous C<sub>3</sub>H mice more than 4 months of age either greatly reduced the incidence or delayed the appearance of mammary tumors.<sup>90</sup> Smaller amounts of testosterone (1 mg. weekly) reduced the incidence of tumors expected when the injections were started early in life, but did not alter the appearance of tumors in multiparous animals.<sup>91</sup> Experiments undertaken in another laboratory also indicate that testosterone propionate in very large amounts will decrease the incidence of mammary tumors in estrogen-treated animals.<sup>65</sup>

Desoxycorticosterone, 2 to 4 mg. per week, induced mammary tumors in male mice.<sup>87</sup> One milligram or less per week did not lead to mammary cancer in male mice of the C<sub>3</sub>H strain or other strains tested, or in female mice.<sup>87</sup>

Progesterone, when administered in large amounts, retarded primary growth. When administered with a known potent estrogen, estrone and 200 µg. progesterone on alternate weeks, the incidence of mammary tumors did not differ from that expected after estrone alone.<sup>88, 89</sup>

Although these hormones to some extent modify some of the effects elicited by estrogens, they have either little or no capacity to reduce or alter the incidence of malignant mammary growth when given in very large doses.

*Hyperplasias, Tumors, and Carcinomas of the Uterus of 1-year-old Animals.*—Atypical and hyperplastic uterine conditions, particularly those classified as glandular cystic hyperplasia and atypical, may follow abnormal ovarian function.<sup>90</sup> The injection of estrogen was reported in intact female monkeys, in some instances associated with cervical tumor, led to hyperplasia and metaplasia of the cervical glands. These lesions did not grow progressively and would revert when progesterone was injected.<sup>90</sup> The uteri tended to become refractory after prolonged treatment.<sup>91</sup>

Atypical hyperplastic or metaplastic lesions of the uterine fibromuscular tissue or of the epithelial tissues of both the uterus and uterine cervix have been referred to. The experimental work undertaken will be divided on that basis for presentation.

*Fibromuscular Reactions.*—Fibromyomatous overgrowths appeared in the subserosa or myometrium of guinea pigs receiving estrogens over prolonged periods. Some of the tumors involved the mucosa, and excessive uterine hemorrhage occurred.<sup>92</sup> Similar lesions have been noted by other investigators.<sup>93, 94</sup>

Fibromyomatous tumors not only occurred on the uterus but also throughout the abdominal cavity.<sup>95</sup> These tumors tended to occur especially in relation to the mesenteries and peritoneum of the spleen and stomach. They were histologically malignant in that they occasionally invaded the pancreas, liver, other viscera, and the body wall.<sup>100</sup> Their site of origin is not definitely known but the peritoneal mesothelium has shown the earliest proliferative lesions.<sup>100, 101</sup> The tumoral reaction occurred in both males and females, although more readily in the latter.<sup>102</sup> A large series of normally occurring estrogens and their esters, as well as stilbestrol and hexesterol, elicited the tumorigenic reaction in guinea pigs. The simultaneous administration of progesterone, desoxycorticosterone, and testosterone prevented the development of the tumors.<sup>103</sup> These tumors are not autonomous growths in that they regress when estrogenic treatment is discontinued. The term tumorigenesis was ap-

plied to the process rather than carcinogenesis.<sup>104</sup> As far as is known similar tumors have not been described in estrogen-treated animals of other species.

*Benign and malignant epithelial tumors* of the uteri of experimental animals rarely appear even after the injection of estrogens. Glandular overgrowths or glandular cystic hyperplasia may appear after the injection of estrogens in rabbits<sup>105</sup> and guinea pigs.<sup>97, 105c</sup> The uteri of estrogen-treated rabbits undergo progressive aseptic infarct necrosis.<sup>105d</sup> Septic inflammatory reactions (pyometra), epithelial metaplasia, and glandular cystic hyperplasia have been frequently described in estrogen-treated rats and mice.<sup>106</sup> It is possible that the uterine metaplasia is secondary to the septic condition which, in mice, occurs following the injection of estrogen.<sup>107</sup> Glandular cystic hyperplasia has been observed in estrogen-treated monkeys,<sup>108</sup> although not consistently.<sup>77, 95c, 109</sup> Lacassagne<sup>110</sup> described a small uterine carcinoma in an estrogen-treated mouse.

*Malignant epithelial growths of the uterine cervixes* of estrogen-treated mice have occurred frequently, and atypical hyperplastic and locally invasive lesions in this area have been studied extensively. These observations are probably of further significance because carcinomas of the uterine cervixes of untreated mice occur rarely.<sup>111</sup>

Three of twenty-seven mice which had received estrogen and cutaneous applications of 1:2:5:6-dibenzanthracene for six to ten months had cervical carcinomas.<sup>112</sup> The largest tumor had invaded the bladder and other pelvic tissues.<sup>55b</sup> At the same time a carcinoma-like overgrowth was described in a mouse which had received estrogen (theelol for eighteen and theelin for six months) for over twenty-four months.<sup>113</sup> This tumor had invaded the muscularis and serosa. Similar lesions were observed among other mice injected with estrone or estradiol benzoate.<sup>52e</sup> Twenty-six of 235 estrogen-treated mice showed either precancerous or cancerlike lesions of the uterine cervix or upper vagina.<sup>114</sup> The cervixes of 128 untreated mice were also studied microscopically. Epithelial irregularities of the upper vaginas and cervixes of both treated and control groups appeared more frequently with advancing age. The more advanced lesions occurred in the estrogen-treated mice. The strain of the mice or the tendency to develop mammary tumors did not alter the tumorous response of the cervix.

One of nineteen cervical lesions was observed in a living mouse which had received estradiol benzoate for 319 days, a total of 10,500 I.U.<sup>115</sup> When this mouse was killed the tumor was transplanted into other mice of the same strain and it grew progressively. The squamous-celled carcinoma had apparently arisen from the cervix but involved the entire pelvis and the lumbar nodes. Three carcinomas and twenty-four invasive epithelial lesions appeared among 134 estrogen-treated mice of four different inbred strains.<sup>116</sup> Four of eight mice which had received

estradiol benzoate and testosterone propionate simultaneously had cervical lesions, of which two were considered malignant.

A high incidence of invasive lesions of the cervical epithelium arose in estrogen-treated mice from groups which tolerated estrogens for extended periods.<sup>117</sup> Over 50 per cent of the forty-four mice had cervical lesions after they had received 16.6  $\mu$ g. of estradiol benzoate weekly for one year or more.

Some investigators have not observed cervical tumors in estrogen-treated mice.<sup>118</sup>

*Summary of Effects of Estrogens on Invasive Epithelial Lesions of the Cervix.*—Estrogens stimulate growth of the female genital tissues but the cervical cancers which appear after prolonged estrogenic treatment arise as local proliferative lesions in otherwise relatively quiescent cervical areas.<sup>114, 116, 118</sup> There is no evidence that inherited or transmitted factors or agents are involved in this neoplastic reaction. The tendency to acquire cervical tumors is not associated with the tendency to acquire mammary tumors. Why the neoplastic response of the mouse's genital tract is limited to the cervix and vaginal fornix is not known. The external os has been most frequently involved in animals with small lesions and presumably the larger growths arose at this location.

The mouse's genital tract with its bicornuate uterus and aglandular cervix differs greatly from that of primates.

*Tumors of the Testes in Estrogen-Treated Mice.*—Estrogenic hormones when administered to males usually resulted in a decrease in the size of the testes. The seminiferous epithelium and the interstitial elements were both reduced and evidence of androgenic activity decreased or disappeared.<sup>119</sup> The gonadotropic hormone in the hypophyses of such animals was decreased.<sup>120</sup>

The administration of estrogens (equilin and estradiol) for prolonged periods resulted in a hypertrophy of and an increased number of glandular interstitial cells in mice of unknown genetic origin.<sup>59, 121</sup> In another laboratory this marked hypertrophy of the interstitial cells was limited to the mice of one inbred strain, which had received either estradiol benzoate or equilin benzoate.<sup>122</sup> Three of the mice receiving equilin benzoate had large circumscribed areas of interstitial cells in their testes. These experiments "indicate that some estrogenic chemicals act upon the pituitary, stimulating the formation of increased amounts of hormone (luteinizing hormone or interstitial cell stimulating hormone) capable of transforming the interstitial cells."<sup>122</sup> Similar nodules were not found in the testes of mice of four other strains similarly treated. Burrows described an estrogen-treated mouse with an adenomatous interstitial cell tumor which showed little of the changes of the seminal vesicles and prostate, usually associated with such estrogen treatment.<sup>123</sup> He assumed that the mouse had become refractory to the estrogen.

More recently testicular tumors have been reported in mice of the A strain which have received either triphenylethylene,<sup>124</sup> estradiol benzoate, or stilbestrol.<sup>125</sup> These tumors, although composed chiefly of large glandular cells, invaded the tunica albuginea and surrounding tissues and the lymph nodes of the lumbar and perirenal regions. Mice of a different strain (C) in another laboratory showed testicular tumors when exposed to estrogens for long periods.<sup>126</sup> Testicular tumors did not appear among animals from two other strains given triphenylethylene or estradiol dipropionate.<sup>124</sup>

The sequence of morphologic changes in the testes of estrogen-treated mice of the A strain has indicated that progressive phases of atypical cells appear, and that several types (generations) of cells may contribute to the same or different tumors.<sup>127a</sup> Testicular tumors have also appeared in mice of the JK strain, which have received triphenylethylene.<sup>127b</sup>

The interstitial cell tumors, even those which have extended to the lymph nodes, apparently elaborate an androgenic substance.<sup>125, 127</sup> The seminal vesicles and prostates of animals with such tumors may be enlarged and filled with secretion in spite of the simultaneous injection of estrogens. The tumors grew when transplanted subcutaneously into other mice of the same strain when estrogens were injected into the hosts.<sup>127</sup>

Nodules of interstitial cells have appeared near the hilus of the testes of mice of the A strain that have received injections of pregnant mare serum for long periods. One testicular tumor appeared in a mouse treated first with estrogen and then with Gonadin (a gonadotropic hormone from mare's serum).<sup>128</sup> A marked hypertrophy and hyperplasia of the interstitial cells occurred in mice treated with prolactin.<sup>129</sup>

Testicular tumors have not been described in estrogen-treated animals of other species. In mice they, like the mammary tumors, appear to be strain-limited. Unlike mammary neoplasms the tendency for tumors of the testes to appear in the hybrid young is transmitted by both males and females.<sup>65</sup> It is interesting that the testicular as well as the mammary and cervical tumors appear after prolonged stimulation and after the tissues have failed to respond in the usual manner or have regressed.

*Male Accessory Glands.*—A great many studies have been undertaken in which lesions of a hypertrophic or metaplastic type have been observed in the prostates and seminal vessels of rats and mice. The simultaneous administration of androgen largely counteracted the effect of the estrogens. Tumors of these tissues have not occurred. The literature has been previously reviewed<sup>1a, 2</sup> and will not be repeated here.

The experiments in which dogs and monkeys have been used, although they have not led to the malignant growths, are of greater interest. Daily injection of 800 to 2,000 I. U. of estrone for five and one-half to seven weeks resulted in an eightfold increase in the size of the prostates

of young dogs.<sup>120</sup> Dogs with "feminizing" testicular tumors had large prostates.<sup>121</sup> The enlarged prostates contained excessive amounts of fibromuscular stroma and glands distended with or lined by a metaplastic stratified squamous epithelium. The extent of epithelial metaplasia was inversely related to the fibromuscular hypertrophy. Smaller doses of estrogen (stilbestrol) reduced the size of the functional or hyperplastic prostate while larger doses enlarged it.<sup>122</sup> The hyperplastic prostates decreased in size following castration.

The injection of estrone caused a marked hypertrophy of the seminal vesicles of immature male monkeys. The epithelium of the prostatic utricle, colliculus seminalis, and cavernous urethra became thickly stratified.<sup>123</sup> The prostatic enlargement was largely attributable to an increase of the utricular tissue.

*Pituitary Tumors Among Estrogen-Treated Animals.*—A sex difference in the size and histology of the hypophysis has been described in several species.<sup>124</sup> Among experimental animals the estrogenic hormones markedly alter the size and structure of the hypophyses of rats and some mice.<sup>125</sup>

Almost simultaneously three different investigators described marked hypophyseal hypertrophy or adenomatous proliferation of the hypophyses in estrogen-treated rats or mice.<sup>127</sup> The chromophobic cells constituted the greater part of the anterior lobes of the enlarged glands of these animals.

Among mice spontaneous tumors of the hypophyses rarely occur.<sup>128</sup> One chromophobic adenoma appeared in a mouse with bilateral ovarian granulosa cell tumors.<sup>129</sup> Marked hypophyseal enlargement rarely occurred among estrogen-treated stock mice (1 in 679),<sup>140</sup> or among estrogen-treated mice of three inbred strains.<sup>132</sup> The tumorous transformation of the hypophyses did not occur in estrogen-treated mice of all strains<sup>56</sup> and could not be associated with the tendency of the different strains to acquire mammary tumors.<sup>141</sup> Hypophyseal tumors appeared frequently only among estrogen-treated mice of one low-mammary tumor strain in one laboratory and not among mice of six other strains similarly treated.<sup>142</sup> Both male and female mice of this strain transmitted the tendency to develop pituitary tumors to their offspring.<sup>53c</sup> The tumors appeared more frequently and at an earlier age in males than in females and attained sufficient size to force the cranial sutures and alter the shape of the head.

All of the pituitary tumors in mice have consisted of chromophobic cells. The smaller tumors usually resemble generalized hyperplasias of the chromophobes. The larger tumors, although not circumscribed, were made up of more hyperplastic cords of chromophobic cells and were probably adenomas. They may be transplanted to other mice of the same strain.<sup>65</sup> Some of the tumors may be a deep red color and contain large sinusoids or even hemorrhagic areas.



Large hypophyseal tumors also appear in rats receiving large amounts of estrogen.<sup>143</sup> The vascular tumors were composed largely of chromophobic cells with large Golgi nets. The few chromophilic cells were largely degranulated.<sup>144</sup> Pituitary tumors have been observed in castrated male rats bearing ovarian grafts.<sup>145</sup>

Small hypophyseal tumors have been observed in a number of untreated rats.<sup>41</sup> These spontaneous tumors have been transplanted into other rats but they only grew when placed in older animals which were found at autopsy to have tumors in their own hypophyses.<sup>146</sup> This observation indicates that these particular tumors, at least, depend upon an environment attained with advanced age, not only for their origin but for their continued growth.

*Lymphoid and Other Tumors in Estrogen-Treated Mice.*—Lymphatic leucemia appears frequently in mice of some inbred strains and rarely in animals of other strains.<sup>147</sup> Lymphoid tumors have appeared in a great many estrogen-treated mice at incidences sufficiently higher than in the untreated control mice to merit consideration. The implication is not made that these hormones are of etiologic significance in spontaneous leucemia.

Three mice among 111 given estradiol benzoate or estrone benzoate died with lymphoid tumors.<sup>52g</sup> These tumors were transplantable.<sup>148</sup> Fourteen mice from four different strains developed lymphoid tumors when estrogens were injected.<sup>149a</sup> Most of the tumors involved the mediastinum. Tumors of this type were not found in untreated animals of these same strains.

Lymphoid tumors appeared in 15.4 per cent (22 of 140) of the mice of the C<sub>3</sub>H strain which had received variable amounts of estrogen. The tumors involved the mediastinum in nearly all cases and frequently many other tissues were invaded or a generalized leucemic picture attained. A similar tumor occurred in 1 of 203 control mice which had received nonestrogenic material or no treatment.<sup>149b</sup> The greater number of tumors appeared among the groups receiving the larger doses of hormone.

The incidence of lymphoid tumors was also increased among mice of another strain when large amounts of estrone were injected<sup>150</sup> or when pellets of stilbestrol were implanted.<sup>126</sup> Others have not noted an increase in the incidence of lymphoid tumors.<sup>53c</sup>

Why estrogens might increase the incidence of lymphoid tumors under such conditions is unknown. Mice treated with x-rays<sup>151</sup> or carcinogens<sup>152</sup> also have shown an increased incidence or earlier appearance of lymphoid tumors. Estrogens will result in atrophy of thymus<sup>153</sup> and probably other lymphoid tissues. Lymphoid tissues are very susceptible to x-rays. It is possible that the malignant transformation of the lymphoid tissue subsequent to the exposure to the different agents mentioned may have some common basis.

*Other Tissues in Which Tumors Have Appeared in Estrogen-Treated Animals.*—A number of investigators have observed spindle-celled sarcomas arising at the sites of injection of oily solutions of estrogens.<sup>154</sup> Some sarcomas have appeared in mice receiving nonestrogenic substances as well.<sup>154c</sup> The incidence of such tumors was low and they have not been reported among mice bearing pellets of estrogens. At this time the significance of these observations might be questioned.

Female mice of one strain showed a very high incidence of bone tumors.<sup>155</sup> The incidence was always higher among the females than among the males, about 75 per cent and 26 per cent showing osteogenic tumors at an average age of 16 to 18 months, respectively. The tumors were frequently multiple and ranged from osteomas to osteogenic sarcomas.<sup>156</sup> The administration of estrone increased the incidence of bone tumors in males and decreased the age at which they appeared in both sexes.<sup>157</sup>

The bones of animals of some species are greatly modified when estrogens are injected. The long bones of chickens and rats may be made increasingly opaque to x-rays and their longitudinal growth depressed.<sup>158</sup> In mice the pubes are partially resorbed and the marrow cavities of the long bones become replaced by compact bone.<sup>159</sup> These changes may be prevented if the androgen, testosterone propionate, is given with the estrogen.<sup>160</sup>

Although these experiments indicate that estrogens may directly or indirectly affect the proliferation of osseous tissues, osteogenic tumors have been reported only by Pybus and Miller.<sup>155-157</sup> This would indicate that, as with the mammary, pituitary, and testicular tumors arising in estrogen-treated animals, specific factors or agents in addition to the hormone are essential.

*The Adrenal Glands in Relation to Experimental Tumors.*—The adrenals are affected, probably indirectly, by the injection of estrogens.<sup>163</sup> These glands have been studied extensively in estrogen-treated mice.<sup>32, 137c, 161</sup> A perimedullary degeneration (brown degeneration) of the cortex occurs in estrogen-treated animals and in untreated mice of some strains.<sup>162</sup> These lesions sometimes involved the medullary areas and were associated with the tendency of the mice of strains bearing them to acquire mammary tumors.<sup>163</sup> Strain differences in the persistence of the X-zone of cancer-resistant and cancer-susceptible strains have been observed.<sup>32, 165</sup>

The adrenal lesions of estrogen-treated male mice were more extensive than those of the females and were correlated with the tendency to have hypophyseal tumors.<sup>54c</sup> Similar adrenal lesions appear in rabbits with mammary or uterine tumors.<sup>43, 44</sup>

*Effect of Sex Hormones on Growth of Tumors.*—Two other aspects of the endocrine-cancer problem are (1) the influence of hormones on tissues after their growth is no longer restricted and (2) the effects of

growing cancers on the genital tissues or functions. The former point is of considerable practical and theoretical significance and will be discussed. It has been mentioned that some tumors of the testes and hypophyses were transplantable only in estrogen-treated animals such as the animals in which they arose. These tumors might either depend on the hormones for their stimulation or directly or indirectly, for the environment created by the hormone. Greene<sup>12-44</sup> has emphasized the acquisition of malignancy which he can demonstrate so well in his rabbits as a series of progressive stages involving hyperplasia, anaplasia, local invasiveness, and finally malignancy and complete autonomy. It might be safe to assume that some tumors, especially the more obviously benign ones, might not survive or proliferate in all environments, while those more obviously malignant, might be autonomous. There is no evidence that sex hormones will alter the rate of growth of mammary adenocarcinomas in mice. Testosterone was without effect.<sup>90, 91</sup> Hypophysectomy did not prevent or greatly reduce the rate of growth of spontaneous mammary tumors.<sup>166</sup>

The growth of transplanted sarcomas was not appreciably changed by the injection of estrogens.<sup>167</sup> Doses of estrogen large enough to induce dwarfism failed to prevent the growth of benzpyrene-induced tumors.<sup>168</sup> One transplanted mammary adenocarcinoma showed inhibited growth and secretory activity when estrogens were injected.<sup>168b</sup>

The growth of the more benign tumors is altered by changes in the environment in which they grow. A transplanted mammary fibroadenoma was largely fibrous when growing in young or aged rats. The incidence of successful grafts was higher in females than in males and was greatly reduced by ovariectomy.<sup>169</sup> Transplanted fibroadenomas grew rapidly in pregnant rats and the epithelial components increased. The growth of other mammary fibroadenomas was not altered by pregnancy<sup>170</sup> nor were sarcomas.<sup>171</sup> The earlier investigations have been reviewed previously.<sup>170</sup> Transplanted mammary fibroadenomas growing in rats receiving testosterone propionate showed a progressive loss of epithelial elements, and some eventually became fibromas.<sup>172</sup>

The resistance of hosts to transplanted tumors partially "immunized" to the transplanted tumors was increased by the injection of estrogen, but not altered by androgen.<sup>173</sup>

#### INTERPRETATION

A large amount of detailed information on the appearance of tumors in experimental animals given estrogens has been recorded. Mammary, uterine, hypophyseal, testicular, lymphoid, and osteogenic tumors appear in animals of some species or strains when they are exposed to estrogens for prolonged periods. Among mice the mammary, hypophyseal, testicular, and osteogenic tumors are restricted by factors or influences transmitted by the maternal parent or parents to their young.

These factors (hereditary or genetic) or influences (milk influence<sup>61</sup> or mammary tumor inciter<sup>62</sup>) restrict the carcinogenic response of specific organs to animals of certain groups. The estrogens are required before these responses may occur. Estrogens, directly or indirectly, affect the tissues giving origin to these tumors, but the tumors appear only in susceptible animals.

The uterine cervical tumors in estrogen-treated mice and to a lesser extent the lymphoid tumors have not revealed, as yet, other accompanying transmitted factors or influences essential for the establishment of these malignancies. This does not mean that they do not exist because all possibilities have not been investigated.

One might search for some common change elicited by estrogens in the different tissues or organs to indicate the mechanism whereby the tumors arise. The growth-stimulating action of estrogen is not adequate to explain the lymphoid tumors or even those of the genital tissues since the tumors of these latter tissues do not appear during the active growth phases but rather after the greater part of the tissue has become somewhat refractory. In other words, it may be that estrogens increase the physiologic age of the tissues so that other factors may facilitate the establishment of malignancy. There is little doubt that continuous and excessive estrogenic treatment will result in changes indicative of tissue damage in the organs in which tumors arise.

It will be difficult to advance some aspects of the problem of the action of estrogens in carcinogenesis until more is known of the mechanism whereby they act on normal cells to augment the anabolic and proliferative functions, and what limits the capacity of these cells to respond. The possibility that estrogens may be altered chemically and that the products formed are carcinogens might be mentioned, but the metabolic derivatives of estrogens are still being investigated.

According to the definition given earlier, estrogens are carcinogenic. There is evidence, however, that they merely facilitate the materialization of certain potentialities which are transmitted to the organism. For practical purposes it might be well to consider them as possibly carcinogenic when administered continuously, although the investigators in these fields may find increasing evidence to doubt their direct participation in malignant transformations of body tissues.

#### REFERENCES

1. (a) Gardner, W. U.: *Arch. Path.* 27: 138, 1939.  
 (b) Lacassagne, A.: *Ergebn. d. Vitamin. u. Hormonforsch.* 2: 259, 1939.  
 (c) Loeb, L.: *J. Nat. Cancer Inst.* 1: 169, 1941.  
 (d) Hartwell, J. L.: "Survey of Compounds Which Have Been Tested for Carcinogenic Activity," National Institute of Health, U. S. Public Health Service, 1941.  
 (e) Allen, E.: *Endocrinology* 30: 942, 1942.
2. Allen, E., and Doisy, E. A.: *J. A. M. A.* 81: 819, 1923.
3. Allen, E., Hisaw, F. L., and Gardner, W. U.: *Sex and Internal Secretions*, Chapt. VIII, *The Endocrine Function of the Ovaries*, Baltimore, 1939, Williams & Wilkins Company.

4. Allen, E.: *Glandular Physiology and Therapy, Physiology of the Ovaries*, Chapt. X, Chicago, 1942, American Medical Association.
5. Emmens, C. W., and Ludford, R. J.: *Nature* 145: 746, 1940.
6. Heckter, O., Lev, M., and Soskin, S.: *Endocrinology* 26: 73, 1940.
7. Lathrop, A. E. C., and Loeb, L.: *J. Cancer Research* 1: 1, 1916.
8. (a) Loeb, L.: *J. Cancer Research* 8: 274, 1924.  
(b) Loeb, L.: *J. Med. Res.* 39: 71, 1918.
9. Loeb, L.: *J. Med. Research* 40: 477, 1919.
10. Cori, C. F.: *J. Exper. Med.* 45: 983, 1927.
11. Murray, W. S.: *J. Cancer Research* 12: 18, 1928.
12. Staff of the Roscoe B. Jackson Memorial Laboratory: *Biology of the Laboratory Mouse*, Philadelphia, 1941, The Blakiston Company.
13. Strong, L. C.: *Cancer Research* 2: 531, 1942.
14. Turner, C. W.: *Sex and Internal Secretions*, Chapt. XI. The Mammary Glands, Baltimore, 1939, Williams & Wilkins Company.
15. (a) Woolley, G., Fekete, E., and Little, C. C.: *Proc. Nat. Acad. Sc.* 25: 277, 1939.  
(b) Idem: *Endocrinology* 28: 341, 1940.  
(c) *Proc. Soc. Exper. Biol. & Med.* 45: 796, 1941.  
(d) *J. Exper. Med.* 74: 1, 1941.
16. Gardner, W. U.: *Cancer Research* 1: 632, 1941.
17. Spiegel, A.: *Virchows Arch. f. path. Anat.* 305: 367, 1939-40.
18. de Jongh, S. E., and Korteweg, R.: *Acta brev. Neerland.* 5: 126, 1935.
19. Lacassagne, A.: *Compt. rend. Acad. d. sc.* 195: 630, 1932.
20. Gardner, W. U.: *Endocrinology* 19: 656, 1935.
21. Murray, W. S.: *Am. J. Cancer* 30: 517, 1937.
22. Furth, J., and Butterworth, J. S.: *Am. J. Cancer* 28: 66, 1936.
23. (a) Lacassagne, A.: *Compt. rend. Soc. de biol.* 115: 927, 1934.  
(b) Harde, E.: *ibid.* 116: 999, 1934.
24. Lacassagne, A.: *Am. J. Cancer* 27: 217, 1936.
25. (a) Loeb, L., and Genther, I. T.: *Proc. Soc. Exper. Biol. & Med.* 25: 809, 1928.  
(b) Suntzeff, V., Burns, E. L., Moskop, M., and Loeb, L.: *Am. J. Cancer* 26: 761, 1936.  
(c) Burns, E. L., Moskop, M., Suntzeff, V., and Loeb, L.: *ibid.* 26: 56, 1936.  
(d) Brunschwig, A., and Bissel, A. D.: *Arch. Surg.* 33: 515, 1936.
26. Bonser, G. M.: *J. Path. & Bact.* 41: 33, 1935.
27. (a) Gibson, L. M.: *J. Cancer Research* 14: 570, 1930.  
(b) Fekete, E.: *Am. J. Path.* 14: 557, 1938.
28. Haaland, M.: *Spontaneous Cancer in Mice. Scientific Report, Imperial Cancer Research Fund, London* 4: 1, 1911.
29. Gardner, W. U., and Strong, L. C.: *Am. J. Cancer* 25: 282, 1935.
30. Gardner, W. U., Strong, L. C., and Smith, G. M.: *Am. J. Cancer* 37: 510, 1939.
31. Van Gulik, P. J., and Korteweg, R.: *Nederl. Akad. v. Wetenschappen. Proc.* 43: 891, 1940.
32. Taylor, H. C., and Waltman, C. A.: *Arch. Surg.* 40: 733, 1940.
33. Gardner, W. U.: *Cancer Research* 1: 345, 1941.
34. (a) Murray, W. S.: *Am. J. Cancer* 20: 573, 1934.  
(b) Bittner, J. J.: *Am. J. Cancer* 25: 614, 1935; (c) *Ibid.*: 25: 791, 1935.
35. Andervont, H. B., and McEleney, W. J.: *Pub. Health Rep.* 54: 1597, 1939.
36. (a) Bagg, H. J.: *Am. Naturalist* 60: 234, 1926.  
(b) Idem: *Am. J. Cancer* 27: 542, 1936.
37. Aub, J. C., Karnofsky, D., and Towne, L. E.: *Cancer Research* 1: 737, 1941.
38. Twombly, G. H., and Taylor, H. C.: *Presented at American Association Cancer Research, Boston*, 1942.
39. Van Gulik, P. J., and Korteweg, R.: *Am. J. Cancer* 38: 506, 1940.
40. Emmens, C. W.: *J. Endocrinol.* 1: 373, 1939.
41. (a) Wolfe, J. M., Burack, E., and Wright, A. W.: *Am. J. Cancer* 38: 385, 1940.  
(b) Idem: *Endocrinology* 27: 883, 1940.  
(c) Wright, A. W., Klinec, C. H., and Wolfe, J. M.: *Am. J. Path.* 16: 817, 1940.
42. (a) Greene, H. S. N.: *J. Exper. Med.* 70: 147, 1939.  
(b) *Ibid.*: 71: 305, 1940.
43. Greene, H. S. N., and Saxton, J. A.: *J. Exper. Med.* 67: 691, 1938.
44. (a) Greene, H. S. N.: *J. Exper. Med.* 65: 809, 1937.  
(b) *Ibid.*: 67: 369, 1938.  
(c) *Ibid.*: 73: 273, 1941.
45. Lipschütz, A.: *Gynéc et obstet.* 36: 408, 481, 1937.
46. Schmidt, I. G.: *Endocrinology* 24: 69, 1939.

47. Pfeiffer, C. A.: *Am. J. Anat.* 58: 195, 1936.
48. Pfeiffer, C. A.: *Anat. Rec.* 75: 465, 1939.
49. (a) Bradbury, J. T.: *Endocrinology* 28: 101, 1941.  
(b) Wilson, J. G.: Thesis, Modification of Reproductive Capacity in Male and Female Rats Treated Prepuberally With Male and Female Sex Hormones, New Haven, 1942, Yale University Graduate School.
50. Goormaghtigh, M., and Amerlinck, A.: *Compt. rend. Soc. de biol.* 103: 527, 1930.
51. (a) Lacassagne, A.: *Compt. rend. Soc. de biol.* 114: 427, 1933.  
(b) Idem: *Paris med.* 25: 233, 1935.
52. (a) Bonser, G. M.: *J. Path. & Bact.* 41: 217, 1935.  
(b) Ibid.: 42: 169, 1936.  
(c) Gardner, W. U., Smith, G. M., Allen, E., and Strong, L. C.: *Arch. Path.* 21: 265, 1936.  
(d) Cramer, W., and Horning, E. S.: *Lancet* 1: 247, 1936.  
(e) Ibid.: 1056, 1936.  
(f) Gardner, W. U., Smith, G. M., Strong, L. C., and Allen, E.: *J. A. M. A.* 107: 656, 1936.  
(g) Gardner, W. U.: Some Fundamental Aspects of the Cancer Problem, Science Press, N. Y., Suppl. 4, p. 67, 1937.  
(h) Sontzeff, V., Burns, E. L., Moskop, M., and Loeb, L.: *Am. J. Cancer* 27: 229, 1936.
53. (a) Biscoff, P., Long, M. L., Rupp, J. J., and Clarke, G. J.: *Cancer Research* 2: 52, 1942.  
(b) Ibid.: 2: 198, 1942.  
(c) Gardner, W. U.: *Cancer Research* 1: 345, 1941.  
(d) Haagenesen, C. D., and Randall, H. T.: *Arch. Path.* 33: 411, 1942.
54. Bonser, G. M., Strickland, L. H., and Connal, K. I.: *J. Path. & Bact.* 45: 709, 1937.
55. (a) Burrows, H.: *Am. J. Cancer* 24: 613, 1935.  
(b) Perry, I. H., and Ginzton, L. L.: *Am. J. Cancer* 29: 680, 1937.
56. (a) Lacassagne, A.: *Am. J. Cancer* 28: 735, 1936.  
(b) Idem: *Compt. rend. Soc. de biol.* 122: 183, 1936.
57. (a) Lacassagne, A.: *Compt. rend. Soc. de biol.* 129: 641, 1938.  
(b) Shimkin, M. B., and Grady, H. G.: *J. Nat. Cancer Inst.* 1: 119, 1940.
58. (a) Robson, J. M., and Bonser, G. M.: *Nature* 142: 836, 1938.  
(b) Gardner, W. U.: Unpublished.
59. (a) Burrows, H.: *Brit. J. Surg.* 23: 191, 1935.  
(b) Idem: *J. Path. & Bact.* 42: 161, 1936.
60. (a) Staff, Jackson Memorial Laboratory, *Science* 78: 465, 1933.  
(b) Korteweg, R.: *Nederl. tijdschr. v. geneesk.* 79: 1482, 1935.
61. (a) Murray, W. S., and Little, C. C.: *Am. J. Cancer* 27: 516, 1936.  
(b) Bittner, J. J.: *Am. J. Cancer* 30: 530, 1937.  
(c) Idem: *Tr. & Stud., Coll. Physicians, Philadelphia* 9: 129, 1941.  
(d) Idem: *J. Nat. Cancer Inst.* 1: 155, 1940.
62. Bittner, J. J.: *Cancer Research* 1: 290, 1941.
63. Twombly, G. H.: *Proc. Soc. Exper. Biol. & Med.* 44: 617, 1940.
64. Burns, E. L., and Schenken, J. R.: *Proc. Soc. Exper. Biol. & Med.* 43: 608, 1940.
65. Gardner, W. U.: Unpublished.
66. (a) Sutzeff, V., Burns, E. L., Moskop, M., and Loeb, L.: *Am. J. Cancer* 27: 229, 1936.  
(b) Gardner.<sup>52g</sup>
67. Gardner, W. U.: *Endocrinology* 28: 53, 1941.
68. Sutzeff, V., Kirtz, M. K., Blumenthal, H. T., and Loeb, L.: *Cancer Research* 1: 446, 1941.
69. McEuen, C. S., Selye, H., and Collip, J. B.: *Lancet* 1: 775, 1936.
70. McEuen, C. S.: *Am. J. Cancer* 36: 551, 1939.
71. Astwood, E. B., and Geschichter, C. F.: *Arch. Surg.* 36: 372, 1938.
72. (a) Geschichter, C. F.: *Science* 89: 35, 1939.  
(b) Idem.: *Radiology* 33: 439, 1939.
73. Geschichter, C. F., and Byrnes, E. W.: *Arch. Path.* 33: 334, 1942.
74. Noble, R. L., McEuen, C. S., and Collip, J. B.: *Canad. M. A. J.* 42: 413, 1940.
75. Noble, R. L., and Collip, J. B.: *Canad. M. A. J.* 44: 1, 1941.
76. Gardner, W. U., and van Wagenen, G.: *Endocrinology* 22: 164, 1938.
77. Hartman, C. G., Geschichter, C. F., and Speert, H.: *Anat. Rec.* 79: 31 (suppl.), 1941.
78. Speert, H.: *Bull. Johns Hopkins Hosp.* 67: 414, 1940.

79. (a) Gardner, W. U., Diddle, A. W., Allen, E., and Strong, L. C.: *Anat. Rec.* 60: 457, 1934.  
(b) Gardner, W. U., Smith, G. M., and Strong, L. C.: *Proc. Soc. Exper. Biol. & Med.* 33: 148, 1935.
80. Cheatle, L.: *Brit. J. Surg.* 22: 710, 1935.
81. (a) Loeb, L., Burns, E. L., Sontzeff, V., and Moskop, M.: *Am. J. Cancer* 30: 47, 1937.  
(b) Loeb, L., and Simpson, R. M.: *Science* 88: 433, 1938.
82. (a) Gomez, E. T., and Turner, C. W.: *Mo. Agr. Exp. Sta. Research Bul. No.* 259, 1937.  
(b) Lewis, A. A., and Turner, C. W.: *Mo. Agr. Exp. Sta. Research Bul. No.* 310, 1939.
83. (a) Gardner, W. U.: *Proc. Soc. Exper. & Med.* 45: 835, 1940.  
(b) Gardner, W. U., and White, A.: *Proc. Soc. Exper. Biol. & Med.* 48: 590, 1941.  
(c) Lyons, W. R., Simpson, M. E., and Evans, H. M.: *Anat. Rec.* 82: 38 (suppl.), 1942.  
(d) Lyons, W. R., and Sako, Y.: *Proc. Soc. Exper. Biol. & Med.* 44: 398, 1940.  
(e) Gardner, W. U., and Chamberlin, T. L.: *Yale J. Biol. & Med.* 13: 641, 1941.
84. Turner, C. W., and Frank, A. H.: *Science* 73: 295, 1931.
85. Turner, C. W., and Gomez, E. T.: *Mo. Agr. Exper. Sta. Bul. No.* 206, 1934.
86. Cole, H. A.: *Proc. Roy. Soc., S.B.* 114: 136, 1933.
87. van Heuverswyn, T., Folley, S. J., and Gardner, W. U.: *Proc. Soc. Exper. Biol. & Med.* 41: 389, 1939.
88. Lacassagne, A.: *Compt. rend. Soc. de biol.* 126: 385, 1937.
89. Lacassagne, A.: *Bull. Assoc. franç. p. l'étude du Cancer* 27: 1, 1938.
90. Nathanson, I. T., and Andervont, H. B.: *Proc. Soc. Exper. Biol. & Med.* 40: 421, 1939.
91. Jones, E. E.: *Cancer Research* 1: 787, 1941.
92. Shimkin, M. B., and Grady, H. G.: *J. Nat. Cancer Inst.* 2: 61, 1941.
93. Gardner, W. U., and Hil, R. T.: *Proc. Soc. Exper. Biol. & Med.* 34: 718, 1936.
94. (a) Burch, J. C., Williams, W. L., and Cunningham, R. S.: *Surg., Gynec. & Obst.* 53: 338, 1931.  
(b) Witherspoon, J. T.: *Surg., Gynec. & Obst.* 61: 743, 1935.  
(c) Idem: *Am. J. Obst. & Gynec.* 31: 173, 1936.
95. (a) Overholser, M. D., and Allen, E.: *Proc. Soc. Exper. Biol. & Med.* 30: 1322, 1936.  
(b) Idem: *Surg., Gynec. & Obst.* 60: 129, 1935.  
(c) Engle, E. T., and Smith, P. E.: *Anat. Rec.* 61: 471, 1935.  
(d) Migliavacca, A.: *Arch. f. Gynäk.* 164: 463, 1937.
96. Hisaw, F. L., and Lendrum, F. C.: *Endocrinology* 20: 228, 1936.
97. (a) Nelson, W. O.: *Anat. Rec.* 68: 99, 1937.  
(b) Idem: *Endocrinology* 24: 50, 1939.
98. (a) Moricard, R., and Chauchoix, J.: *Compt. rend. Soc. de biol.* 129: 556, 1938.  
(b) Idem: *Gynec. & Obst.* 27: 272, 1938.  
(c) Dessau, F.: *Arch. internat. pharmacodyn. et de therap.* 55: 402, 1937.  
(d) Idem: 58: 344, 1938.
99. Lipschütz, A., and Iglesias, R.: *Compt. rend. Soc. de biol.* 129: 519, 1938.
100. (a) Lipschütz, A., and Vargas, L.: *Cancer Research* 1: 236, 1941.  
(b) Lipschütz, A., Thibaut, R., and Vargas, L.: *Cancer Research* 2: 45, 1942.  
(c) Vargas, L., and Lipschütz, A.: *Compt. rend. Soc. de biol.* 129: 810, 1938.
101. Woodruff, L. M.: *Cancer Research* 1: 367, 1941.
102. Lipschütz, A., Vargas, L., and Palma, J.: *Cancer Research* 1: 575, 1941.
103. Lipschütz, A., Vera, O., and Gonzalez, S.: *Cancer Research* 2: 204, 1942.
104. Lipschütz, A., and Vargas, L.: *Lancet* 1: 1313, 1939.
105. (a) Pearson, H.: *Ztschr. f. Krebsforsch.* 41: 103, 1934.  
(b) Ibid.: 46: 109, 1937.  
(c) Lipschütz, A., Vargas, L., Jr., Jedlicky, A. and Bellolig, P.: *Am. J. Cancer* 39: 185, 1940.  
(d) Zondek, B.: *J. Exper. Med.* 63: 789, 1936.
106. (a) Selye, H., Thompson, D. L., and Collip, J. B.: *Nature* 135: 65, 1935.  
(b) McEuen, C. S.: *Am. J. Cancer* 27: 91, 1936.  
(c) Zondek, B.: *Am. J. Obst. & Gynec.* 33: 979, 1937. Other references see (1a).
107. (a) Weinstein, L., Gardner, W. U., and Allen, E.: *Proc. Soc. Exper. Biol. & Med.* 37: 391, 1937.  
(b) Gardner, W. U., and Allen, E.: *Endocrinology* 21: 727, 1937.

108. (a) Zuckerman, S., and Morse, A. H.: *Surg., Gynec. & Obst.* 61: 15, 1935.  
 (b) Zuckerman, S.: *J. Obst. & Gynec.* *Brit. Emp.* 41: 194, 1937.
109. Gardner, W. U., and van Wagenen, G.: *Anat. Rec.* 70: 29 (suppl.), 1938.
110. Lacassagne, A.: *Compt. rend. Soc. de biol.* 121: 697, 1936.
111. Slye, M., Holmes, H. F., and Wells, H. G.: *J. Cancer Research* 8: 95, 1924.
112. Perry, I. H.: *Proc. Soc. Exper. Biol. & Med.* 35: 325, 1936.
113. Loeb, L., Burns, E. L., Suntzeff, V., and Moskop, M.: *Proc. Soc. Exper. Biol. & Med.* 35: 329, 1936.
114. Suntzeff, V., Burns, E. L., Moskop, M., and Loeb, L.: *Am. J. Cancer* 32: 256, 1938.
115. Gardner, W. U., Allen, E., Smith, G. M., and Strong, L. C.: *J. A. M. A.* 110: 1182, 1938.
116. Gardner, W. U., and Allen, E.: *Yale J. Biol. & Med.* 12: 213, 1939.
117. Allen, E., and Gardner, W. U.: *Cancer Research* 1: 359, 1941.
118. (a) Loeb, L., Suntzeff, V., and Burns, E. L.: *Science* 88: 132, 1938.  
 (b) *Am. J. Cancer* 34: 113, 1938.
119. Moore, C. R., and Price, D.: *Am. J. Anat.* 50: 13, 1932.
120. Meyer, R. K., Leonard, S. L., Hisaw, F. L., and Martin, S. J.: *Proc. Soc. Exper. Biol. & Med.* 27: 702, 1930.
121. Burrows, H.: *J. Path. & Bact.* 41: 218, 1935.
122. (a) Gardner, W. U.: *Anat. Rec.* 67: 49 (suppl.), 1936.  
 (b) *Ibid.*: 68: 339, 1937.
123. Burrows, H.: *J. Path. & Bact.* 44: 699, 1937.
124. Bonser, G. M., and Robson, J. M.: *J. Path. & Bact.* 51: 9, 1940.
125. Hooker, C. W., Gardner, W. U., and Pfeiffer, C. A.: *J. A. M. A.* 115: 443, 1940.
126. Shinkin, M. B., Grady, H. G., and Andervont, H. B.: *J. Nat. Cancer Inst.* 2: 65, 1941.
127. (a) Hooker, C. W., and Pfeiffer, C. A.: *Cancer Research* 2: 759, 1942.  
 (b) Gardner, W. U.: *Cancer Research* 3: 92, 1943.
128. Pfeiffer, C. A., and Hooker, C. W.: *Cancer Research* 3: 124, 1943.
129. Champy, C., Wolff, R., and Coujard-Champy, C.: *Compt. rend. Soc. de biol.* 130: 413, 1930.
130. (a) de Jongh, S. E., and Koh, D. S.: *Acta brev. Neerl.* and 5: 177, 1935.  
 (b) *Ibid.*: 6: 46, 1936.
131. (a) Greulich, W. W., and Burford, T. H.: *Am. J. Cancer* 28: 496, 1936.  
 (b) Zuckerman, S., and Groome, J. R.: *J. Path. & Bact.* 46: 7, 1938.
132. Huggins, C., and Clark, P. J.: *J. Exper. Med.* 72: 747, 1910.
133. (a) van Wagenen, G.: *Anat. Rec.* 63: 367, 1935.  
 (b) Parker, N. S., and Zuckerman, S.: *Lancet* 1: 925, 1935.  
 (c) Courrier, R., and Gros, G.: *Compt. rend. Soc. de biol.* 118: 686, 1935.
134. (a) Zuckerman, S.: *J. Anat.* 72: 261, 1938.  
 (b) *Idem*: *Lancet* 1: 135, 1936.
135. Sevringhaus, A. E.: *Sex and Internal Secretions*, Chapt. XIX, Anterior Hypophyseal Cytology in Relation to the Reproduction Hormones, Baltimore, 1939, Williams & Wilkins Company.
136. (a) Hohlweg, W.: *Klin. Wchnschr.* 13: 92, 1934.  
 (b) Wolfe, J. M.: *Proc. Soc. Exper. Biol. & Med.* 32: 757, 1192, 1935.  
 (c) Selye, H., Collip, J. B., and Thompson, D. L.: *Proc. Soc. Exper. Biol. & Med.* 30: 1377, 1935.
137. (a) Zondek, B.: *Lancet* 1: 776, 1936.  
 (b) McEuen, C. S., Selye, H., and Collip, J. B.: *Lancet* 1: 995, 1936.  
 (c) Cramer, W., and Horning, E. S.: *Lancet* 1: 247, 1936.
138. Slye, M., Holmes, H. F., and Wells, H. G.: *Am. J. Cancer* 15: 1387, 1931.
139. Gardner, W. U., Smith, G. M., and Strong, L. C.: *Am. J. Cancer* 26: 541, 1936.
140. Burrows, H.: *Am. J. Cancer* 28: 741, 1936.
141. Lacassagne, A.: *Compt. rend. Soc. de biol.* 126: 112, 1937.
142. Gardner, W. U.: *Yale J. Biol. & Med.* 12: 544, 1940.
143. Zondek, B.: *Am. J. Cancer* 33: 555, 1938.
144. Weil, A., and Zondek, B.: *Endocrinology* 25: 114, 1939.
145. Oberling, C., and Guerin, P.: *Compt. rend. Soc. de biol.* 123: 1152, 1936.
146. Saxton, J. A.: *Cancer Research* 1: 277, 1941.
147. Richter, M. N., and MacDowell, E. C.: *Physiol. Rev.* 15: 509, 1935.
148. Lawrence, J. H., and Gardner, W. U.: *Am. J. Cancer* 33: 112, 1938.
149. (a) Lacassagne, A.: *Compt. rend. Soc. de biol.* 126: 193, 1938.  
 (b) Gardner, W. U., Kirschbaum, A., and Strong, L. C.: *Arch. Path.* 29: 1, 1940.



150. Bischoff, F., Long, M. L., Rupp, J. J., and Clark, G. J.: *Endocrinology* 28: 789, 1941.
151. Furth, J., and Furth, O. B.: *Am. J. Cancer* 28: 54, 1936.
152. Morton, J. J., and Milder, G. B.: *Science* 87: 327, 1938.
153. Schacher, J., Browne, J. S. L., and Selye, H.: *Proc. Soc. Exper. Biol. & Med.* 36: 488, 1937.
154. (a) Gardner, W. U., Smith, G. M., Strong, L. C., and Allen, E.: *Arch. Path.* 21: 504, 1936.  
 (b) Lacassagne, A.: *Compt. rend. Soc. de biol.* 126: 190, 1937.  
 (c) Burns, E. L., Suntzeff, V., and Loeb, L.: *Am. J. Cancer* 32: 534, 1938.
155. Pybus, F. C., and Miller, E. W.: *Am. J. Cancer* 34: 348, 252, 1938.
156. Pybus, F. C., and Miller, E. W.: *Am. J. Cancer* 40: 47, 54, 1940.
157. Pybus, F. C., and Miller, E. W.: *Nature* 142: 872, 1938.
158. (a) Zondek, B.: *Lancet* 2: 842, 1936.  
 (b) Idem: *Folia clin. orient.* 1: 1, 1937.
159. (a) Gardner, W. U.: *Am. J. Anat.* 59: 459, 1936.  
 (b) Gardner, W. U., and Pfeiffer, C. A.: *Proc. Soc. Exper. Biol. & Med.* 37: 678, 1938.
160. Gardner, W. U., and Pfeiffer, C. A.: *Proc. Soc. Exper. Biol. & Med.* 38: 599, 1938.
161. (a) Burrows, H.: *J. Path. & Bact.* 43: 121, 1936.  
 (b) Lacassagne, A., and Reynaud, A.: *Compt. rend. Soc. de biol.* 124: 1183, 1187, 1937.
162. Cramer, W., and Horning, E. S.: *J. Path. & Bact.* 44: 633, 1937.
163. Cramer, W., and Horning, E. S.: *Am. J. Cancer* 37: 343, 1939.
164. Blaisdell, J. S., Gardner, W. U., and Strong, L. C.: *Cancer Research* 1: 283, 1941.
165. Daughaday, W.: *Cancer Research* 1: 883, 1941.
166. Gardner, W. U.: *Cancer Research* 2: 476, 1942.
167. Bischoff, F., and Maxwell, L. C.: *Am. J. Cancer* 27: 87, 1936.
168. (a) Zondek, B.: *Lancet* 1: 689, 1937.  
 (b) Eisen, M. J.: *Cancer Research* 1: 457, 1941.
169. (a) Heiman, J.: *Am. J. Cancer* 22: 497, 1934.  
 (b) Heiman, J., and Krebhiel, O. F.: *ibid.* 27: 450, 1936.
170. Emge, L. A.: *Am. J. Obst. & Gynec.* 28: 682, 1934.
171. Emge, L. A., Schilling, W., and Sulff, L. M. R.: *Proc. Soc. Exper. Biol. & Med.* 38: 388, 1938.
172. (a) Heiman, J.: *J. Cancer* 39: 172, 1940.  
 (b) Mohs, F. E.: *Cancer Research* 1: 151, 1941.
173. (a) Nathanson, I. T., and Salter, W. T.: *Arch. Path.* 27: 828, 1938.  
 (b) Salter, W. T., Nathanson, I. T., and Wilson, H.: *Cancer Research* 1: 60, 1941.
174. (a) Woolley, G. W., Law, L. W., and Little, C. C.: *Cancer Research* 1: 955, 1941.  
 (b) Bfyan, W. R., Kahler, H., Shimkin, M. B., and Andervont, H. B.: *J. Nat. Cancer Inst.* 2: 451, 1942.

## EXPERIMENTAL INVESTIGATIONS CONCERNING THE ROLE OF THE PITUITARY IN TUMORIGENESIS

HANS SELYE, M.D., PH.D., D.Sc., F.R.S.(C), MONTREAL, QUE.

THE main object of this review is to survey the experimental medical literature concerning the influence of the hypophysis on tumorigenesis in general and the role of hormones in eliciting tumor formation in the pituitary itself. Accordingly, we shall subdivide our material into two principal sections; the first will be concerned with the effect on tumor formation of deficiency or excess of pituitary hormones, while the second will deal with the formation of pituitary tumors in animals treated with hormones of other glands. A brief additional section will be devoted to the few available data on morphologic changes in the anterior lobe elicited by experimental tumors.

### EFFECT OF THE PITUITARY ON TUMOR FORMATION

Since the pituitary is largely responsible for somatic growth in general, it has often been assumed that the "growth hormone," produced by this gland, may play an important part in pathologic growth as well. Yet experiments designed to demonstrate a definite action of the anterior lobe on experimental tumorigenesis have been rather disappointing. This is perhaps not as surprising as it may appear at first sight. The growth of individual organs and tissues is not seriously inhibited by *hypophysectomy*. Thus we found,<sup>107</sup> and several other investigators<sup>33, 34, 78, 116</sup> confirmed, that the regeneration of kidney tissue following partial nephrectomy, as well as the healing of skin wounds, is not prevented by hypophysectomy even though somatic growth ceases. This, we felt, indicates that the hypophysis determines only the proportionate increase in the size of the body as a whole but has comparatively little effect on the growth-promoting action of stimuli affecting individual cell groups. Since tumor cells are notoriously independent of the rest of the soma, it is perhaps understandable that they are not specifically dependent upon hypophyseal control, except secondarily inasmuch as the pituitary hormones influence the tissues of the host organism in which the tumor cell lives.

In view of these considerations it does not appear profitable to devote a great deal of space to a critical discussion of the numerous theories concerning the influence of the hypophyseal hormones on tumorigenesis and we shall limit ourselves to a brief survey of the relevant facts reported in the literature.

Let us consider first the effect of experimentally induced pituitary deficiency.

In the guinea pig Vargas<sup>11</sup> noted that hypophysectomy does not prevent the production of peritoneal fibromatosis by estradiol.

In the mouse x-ray treatment of the pituitary region retards the growth of spontaneous mammary carcinomata in cancer-susceptible strains, especially if the tumor appears at the period of maximum body weight retardation.<sup>15</sup> In hypophysectomized mice Korteweg and Thomas,<sup>55, 56</sup> found that the growth of transplantable and 3,4-benzpyrene tumors is retarded. On the other hand, Gardner<sup>32</sup> noted that in mice hypophysectomized during pregnancy or lactation, mammary cancers can develop even after ablation of the hypophysis.

In the rabbit Lascassagne and Nyka<sup>62</sup> were unable to influence the growth of transplantable carcinomas by pituitary destruction.

In the rat Bischoff and his associates<sup>13, 15</sup> found that roentgen and radon irradiation of the pituitary region significantly retards the growth of transplantable rat sarcoma "R 10" and "carcinoma 256." In the case of the carcinoma the growth rate of the tumor is restored by anterior lobe extracts. Hypophysectomy also retards the growth of the Walker rat tumor.<sup>4, 72, 98</sup> Irradiation of the pituitary is much less effective in this respect.<sup>97</sup> The retardation of the tumor growth rate is approximately the same, however, if the hosts are inadequately fed, so that their body weight increase is inhibited to the same extent as by hypophysectomy.<sup>77</sup> Tumors, produced by subcutaneous injection of dibenzanthracene, also show a decreased growth rate in the hypophysectomized rat.<sup>3</sup> The growth of the Jensen sarcoma is likewise inhibited by hypophysectomy but restored by subsequent anterior lobe therapy. At the same time the O<sub>2</sub> consumption of the tumor is decreased while the anaerobic glycolysis remains normal.<sup>91-93</sup> The glycogen content of the "Walker 256" tumor is inversely correlated with its growth rate and is increased by hypophysectomy.<sup>5</sup> In the case of rat sarcoma "E-2" and "E-5" the retardation in the growth rate following hypophysectomy is not very evident and Franseen and McTiernan<sup>31</sup> were unable to detect any difference in the metabolism of Walker tumors taken from normal and hypophysectomized rats. Mori<sup>53</sup> believed that he saw some inhibition of tumor growth after hypophysectomy, but gave no details.

It should be mentioned in this connection that hypophysectomy facilitates the production of uterine metaplasia by steroid hormones. While in normal rats this lesion is only produced by estrane derivatives, in hypophysectomized rats, androstane and even pregnane derivatives may cause such metaplasia.<sup>105</sup> The question arises whether this change in susceptibility is due to a derailment in steroid metabolism which would lead to a transformation of the androstane and pregnane molecule into more "tumorigenic" compounds.

The development of deciduomas is inhibited by hypophysectomy, but the growth of placenta tissue may proceed in the absence of the pituitary apparently because it is governed by hormones produced by the placental cells themselves.<sup>101</sup>

In man, Lambadarides<sup>61</sup> claimed to have noted some improvement after irradiation of the pituitary region in patients suffering from various types of cancer.

The effect of *pituitary hormone administration* on tumorigenesis has been reviewed by Möller,<sup>52</sup> Grassmann,<sup>53</sup> Lacassagne,<sup>60</sup> and Mori and Nakamura.<sup>54</sup>

In the fowl Sugiura and Benedict<sup>110</sup> were unable to influence the growth of "sarcoma 1" by various pituitary extracts.

In the guinea pig Hofbauer<sup>46,48</sup> found that "leucoplakia" (interpreted as a precancerous change) develops in the cervix uteri under the influence of various anterior lobe preparations.

In the mouse Gross<sup>36</sup> claimed that the growth of transplantable sarcomas is apparently accelerated by certain pregnancy urine extracts, while human placenta implants retard it. The results of subsequent investigators<sup>44, 99, 100, 114</sup> were rather contradictory and difficult to interpret. Sugiura and Benedict<sup>110</sup> state that the Bashford mouse "carcinoma 63" is not influenced by anterior lobe preparations. Bischoff and co-workers<sup>15</sup> state that growth hormone preparations have no clear-cut effect on mouse "sarcoma 180" and similar negative results have been reported concerning the same tumor by giving posterior lobe extracts.<sup>70</sup> Zondek and associates<sup>122</sup> claimed that a mixture of F.S.II. (follicle stimulating hormone) and L.H. (lutinizing hormone) prepared from urine, exerts a significant inhibiting effect on Ehrlich's mouse carcinoma. This was confirmed by many others.<sup>18, 28, 29, 67, 68</sup> Krehbiel and co-workers<sup>68</sup> were unable, however, to influence the growth of mouse "sarcoma 180" by gonadotropic preparations. According to Lustig and Wachtel,<sup>66</sup> even posterior lobe extracts exert an inhibitory effect on certain transplantable mouse tumors, but this is hardly a specific effect and may merely be due to the toxicity of these preparations.

The spontaneous mammary carcinomas of the mouse are not influenced by doses of gonadotropic pregnancy urine preparations sufficient to cause a pronounced enlargement of the ovaries. These experiments, performed by Bischoff and Long<sup>9</sup> on the Marsh-Buffalo strain, led them to conclude that carcinogenesis induced by exogenous folliculoid hormones or estrogens may be without physiologic significance. It must be kept in mind, however, that under the influence of such treatment the ovary would secrete other hormones as well as folliculoids and these other principles (for example, progesterone) may have an anticarcinogenic action. Later, Bischoff and co-workers<sup>10, 11</sup> found that F.S.H. delays the onset of carcinogenesis, while L.H. has no such effect in this strain, although both preparations stimulate mammary growth.

Transplants of anterior lobe tissue increase mammary tumorigenesis, but only in strains having a fair degree of hereditary susceptibility. They are ineffective after ovariectomy.<sup>64, 65</sup> Cramer and Horning<sup>23</sup> claimed that thyrotropic extracts exert an inhibitory action on the development of "R III" strain breast cancers but this could not be confirmed by Haagensen and his associates<sup>42</sup> and it appears probable that the effect of the thyrotropic hormone is merely due to interference with breeding, and in the nonbreeders of course the carcinoma rate is comparatively low.<sup>19, 20</sup> Lacassagne<sup>61</sup> clearly showed that the mammary carcinogenesis obtainable by folliculoids in the susceptible "R III" strain is not inhibitable by thyrotropic hormone treatment. The entire question is quite unsettled, however, since Bischoff and associates<sup>16</sup> report more recently that they were unable to influence mammary carcinogenesis in Marsh-Buffalo mice receiving chronic treatment with pregnant mare serum or sheep anterior lobe extracts, irrespective of whether the treatment caused pronounced ovarian enlargement or gonadal atrophy due to antihormone formation.

The effect of anterior lobe preparations on uterine carcinogenesis has not been adequately studied in the mouse but Loeb and Kirtz<sup>65</sup> state that precancerous lesions in the cervix have been observed repeatedly after anterior lobe transplantations.

In the case of tar cancers gonadotropic pregnancy urine extracts exert no favorable effect,<sup>52</sup> although Katz<sup>54</sup> claimed to have noted an inhibitory and Zeldenrust<sup>117</sup> a stimulating action. Anterior lobe extracts inhibit the growth of such tumors according to Vassiliadis,<sup>112</sup> but it is highly probable that the observed effects were not due to specific hormone actions.

In the rabbit Seel<sup>100</sup> claimed that posterior lobe extracts delay the development of tar cancers and a similar inhibitory effect of posterior lobe preparations has been described by Narimatsu<sup>85</sup> for Kato's transplantable rabbit sarcomas. On the other hand the transplantable Shope papillomas of the rabbit are not influenced by various anterior lobe preparations.<sup>24</sup> Pierson<sup>88</sup> observed a variety of uterine tumors in rabbits chronically treated with gonadotropic pregnancy urine extract. Most of these were characterized by the formation of adenomatous endometrial polyps. Furthermore, the endometrium grew through the uterine wall so that finally it emerged under the serosa resembling the condition of endometriosis. Although such tumors may appear spontaneously in rabbits,<sup>69, 89, 109, 113</sup> they are extremely rare so that there is little doubt of their having been due to the gonadotropic hormone treatment in the previously mentioned experimental series.

In the rat Bischoff and associates<sup>13, 14</sup> noted a slight increase in the growth rate of "transplantable sarcomas and carcinomas" following treatment with crude anterior lobe extracts, but they gave no details. Wiesner and Haddow<sup>115</sup> stated that Jensen sarcomas are not signifi-

cantly influenced by anterior lobe preparations, while gonadotropic pregnancy urine extracts tend to stimulate their growth. Sugiura and Benedict<sup>110</sup> were unable to influence the growth of the Sugiura rat sarcoma, the Flexner-Jobling sarcoma, or the Jensen sarcoma by anterior lobe preparations. Reiss<sup>11</sup> and co-workers<sup>63</sup> claimed that gonadotropic preparations made from pregnancy urine tend to inhibit the growth of Jensen sarcomas while anterior lobe growth hormone extracts slightly stimulate it. Indeed, Baroni and associates<sup>6</sup> state that the growth of the Jensen sarcoma is stimulated by posterior, as well as by anterior lobe extracts. Magath and Smoilowskaia<sup>64</sup> confirmed the inhibitory action of gonadotropic pregnancy urine extracts on these tumors. Druckrey<sup>25</sup> pointed out, however, that the inhibitory effect is more marked in impure than in highly purified extracts of this type. The growth of sarcomas "E-2" and "E-5" do not appear to be stimulated by growth hormone preparations.<sup>27</sup> The results obtained by Robertson and Burnett<sup>34, 35</sup> concerning the action of anterior lobe extracts on transplantable rat carcinomas gave no clear-cut results. Biscoff and Maxwell<sup>12</sup> concluded that "Pronounced gonad stimulation by pituitary extracts and by activated prolan as measured by 300 per cent increases in ovarian and seminal vesicle weights failed to affect the growth of sarcomas R 10 and 180." Heiman<sup>45</sup> claimed that in female rats, gonadotropic pregnancy urine extracts cause a slight decrease and in males a considerable increase in the incidence of takes following transplantation of mammary fibroadenoma tissue.

In vitro the fibroblasts of rat sarcoma tissue grow equally well in a medium containing pituitary extract as in one to which embryonic extract has been added.<sup>2</sup> Long-continued injections of pituitary or pregnancy urine gonadotropic extracts may result in the formation of adenomatous or fibroadenomatous growths in the rat.<sup>50</sup>

In man no striking effect was obtained by the administration of posterior lobe extracts to carcinomatous patients.<sup>19</sup> On the other hand Hübcher<sup>51</sup> described the case of a woman with an adenocarcinoma of the ovary in whom the growth of the tumor was greatly stimulated by a gonadotropic extract of pregnancy urine.

Summarizing the results discussed in this section it may be said that there is no definite evidence of any direct action of pituitary hormones on tumorigenesis. It is well established however that through its effect on the steroid hormone-producing glands, the hypophysis may exert an important indirect effect upon the growth of tumors and on the condition of the host's tissues.

#### PRODUCTION OF PITUITARY TUMORS BY HORMONE TREATMENT

The most dramatic effect of hormones on the development of pituitary tumors is that elicited by the folliculoid compounds. In 1936, Cramer and Horning<sup>21, 22</sup> noted that in the mouse a marked enlarge-

ment of the pituitary with the formation of chromophobe adenomas is obtained following continued treatment with folliculoids. Even in those animals in which actual tumors did not occur, the chromophil cells lost their granules so that almost the entire anterior lobe consisted of chromophil cells. The greatly enlarged anterior lobe of these animals showed numerous hemorrhages and generalized hyperemia. Independently, and almost simultaneously, we were able to show<sup>106</sup> that in rats daily administration of 500 gamma of estrone practically doubles hypophyseal weight within twelve days, and that occasionally this treatment may lead to the formation of cavernous anterior lobe adenomas.<sup>77</sup> These observations have repeatedly been confirmed with folliculoid estrone and stilbene derivatives.<sup>26, 56, 57, 119-121</sup> Zondek's attempt to transplant these adenomas proved unsuccessful.<sup>121</sup> Nelson<sup>56</sup> made a particularly detailed and instructive study of these tumors describing the functional changes (visual disturbances, nystagmus, ataxia, etc.) which result from the pressure exerted by these large tumors on the brain. Curiously, the rabbit does not appear to respond in this manner since Zondek<sup>119</sup> and Mazer and co-workers<sup>71</sup> state that even massive doses of folliculoids cause no significant enlargement of the hypophysis in this species. It is perhaps worth mentioning that in rats receiving prolonged treatment with folliculoids, pigmented adenomas of the intermediate lobe have also been observed.<sup>54, 75</sup> In view of the great rarity of intermediate lobe tumors in human pathology, these observations deserve some attention even though the incidence of middle lobe tumors in folliculoid treated animals is extremely low in comparison with the almost constant development of anterior lobe tumors under similar experimental conditions.

The production of anterior lobe tumors with folliculoid hormones is one of the most obvious experimental facts showing the existence of a definite correlation between the hypophysis and tumorigenesis. As stated in the first part of this review neither pituitary deficiency nor overdosage with hypophyseal hormones exerts any very constant and significant effect on tumor growth except perhaps through the intermediary of steroid hormones which are liberated from other endocrine glands under the influence of hypophyseal hormones. In this sense, for instance, the well-known effect of the folliculoids on mammary tumorigenesis in the mouse may be regarded as under pituitary control since the formation of folliculoids by the ovary is regulated by gonadotropic hormones. The production of hypophyseal adenomas on the other hand is apparently a direct effect of the folliculoid compounds and because of the regularity of its appearance serves as an excellent test object for the study of pituitary tumorigenesis in general. It is for this reason that these growths deserve special attention.

It is well known that a large number of steroid hormones possess an "antifolliculoid" effect, that is to say, are capable of inhibiting certain

folliculoid actions. This potency of steroids has been discussed elsewhere in detail<sup>103, 104</sup> so that here it will only be necessary to summarize those aspects of the problem which are pertinent to the subject of pituitary tumorigenesis. It has been found that most, if not all, hormonally active steroids, other than the folliculoid estrane derivatives, are antifolliculoid to some extent. Thus, they can inhibit the vaginal cornification, the involution of the seminiferous epithelium, and the uterine estrus as well as the enlargement of the adrenal cortex and pituitary which are normally elicited by folliculoids. While only this latter effect is of interest in connection with the problem under discussion, it must be emphasized that there is no close parallelism between the various antifolliculoid actions of the individual steroids. A compound may be very active in inhibiting one, but comparatively inert with regard to another folliculoid action. From the practical, clinical point of view it would obviously be of great interest to detect steroids which have a specific antitumorigenic action.

A large number of steroids have been studied in our laboratory for their ability to inhibit tumorous growth using the hypophyseal enlargement and tumorigenesis elicited by  $\alpha$ -estradiol, as a test object. It soon became evident that testosterone is very active in this respect.<sup>102</sup> Subsequent investigations confirmed this effect of testosterone and showed that methyl-testosterone is approximately equally active while  $\Delta^5$ -androstene-3( $\beta$ ),17( $\alpha$ )-diol,  $\Delta^5$ -androstene-3( $\beta$ )-ol-17-one, and progesterone are considerably less active.<sup>1</sup> A very large number of hitherto unpublished experiments with a great variety of steroids revealed that the dipropionate of  $\Delta^5$ -androstene-3( $\beta$ ),17( $\alpha$ )-diol is somewhat more active than the free compound and that  $\Delta^4$ -androstene-3,17-dione is perhaps one of the most active compounds so far examined. It is of particular interest that  $\Delta^4$ -androstene-3-one-17( $\beta$ )-ol ("cis-testosterone")—which is practically inert as an "androgenic" or testoid compound and is extremely inert with regard to all other hormone actions—is among the most potent compounds when tested for its ability to inhibit the effect of estradiol on the pituitary. This action is even more pronounced in the case of the acetate and propionate of this steroid.

There is, of course, no definite proof indicating that the naturally occurring anterior lobe tumors are caused by stimuli similar to those which are responsible for the tumorigenic effect of the folliculoids. Indeed, physiologically there are some striking differences in symptomatology. Animals which develop anterior lobe tumors as a result of estradiol treatment have an enlarged adrenal cortex, a tendency toward the diabetic type of carbohydrate metabolism disturbance, definite abnormalities in the development and function of their sex organs, and manifestations due to the local pressure which the enlarged hypophysis exerts on the brain tissue.

It is very probable that these tumorous anterior lobes are capable of producing an excess of certain pituitary hormones especially the



adrenotropic, mammotropic, lactogenic and, perhaps, also diabetogenic factors. On the other hand, judged by the inhibition of somatic growth and the atrophy of the thyroid and gonads, they appear to discharge subnormal amounts of growth-promoting thyrotropic and gonadotropic principles. Especially the inhibition of somatic growth is rather different from the manifestations of hyperactive anterior lobe tumors in man. Yet, even in human pathology the functional manifestations differ depending upon the type of tumorous growth, and the resemblance between these experimental tumors and the spontaneous anterior lobe adenomas of man is sufficiently great to make experimental work concerning inhibition of the rat tumors appear to be of some possible clinical applicability. From this point of view the activity of cistosterone and its esters is of special interest because these compounds appear to exert a pronounced antitumorigenic action uncontaminated by any significant degree of undesirable hormonal side-effects.

#### MORPHOLOGIC CHANGES IN THE ANTERIOR LOBE ELICITED BY EXPERIMENTAL TUMORS

Before discussing the experimental literature it may be well, for the sake of comparison, to survey briefly the data concerning hypophyseal changes in tumor-bearing patients.

Tumors of various organs may influence the structure of the pituitary gland. Thus in patients suffering from carcinomas, Karlefors<sup>53</sup> noted a decrease in the eosinophiles and an increase in the main cells. Krieger<sup>59</sup> found that the average weight of the gland is relatively high in cases of malignant tumors. Berblinger and Muth<sup>8</sup> noted an increase in main cells in cases of carcinoma or sarcoma, but they did not consider this to be a specific change and looked upon it merely as the effect of toxic products liberated from the tumor tissue. Saenger<sup>66</sup> observed a tumorlike proliferation of the main cells in the hypophysis of a woman with a large ovarian carcinoma. It seems questionable, however, whether this change should be attributed to the tumor as such, because the patient showed other signs of endocrine disturbances. Puccinelli<sup>90</sup> emphasized the occurrence of large quantities of pigment in the posterior lobe of tumor-bearing individuals. Kraus and Traube<sup>57</sup> state that in carcinoma-cachexia the number of basophiles is usually subnormal. Meessen<sup>79</sup> claimed that in carcinomatous patients, there is increased basophilic invasion in the posterior lobe.

Chorion epitheliomas in man occupy a particular position in so far as they produce gonadotropic hormones. Zondek<sup>118</sup> was the first to note that in such cases the pituitary shows pregnancy changes, a fact which has been confirmed by Erdheim<sup>30</sup> and Siegmund.<sup>108</sup>

With regard to experimental tumors the following observations are noteworthy. Berblinger<sup>7</sup> and Berblinger and Muth<sup>8</sup> showed that treatment with various protein extracts may lead to such changes in the rabbit pituitary as have been seen in carcinoma-bearing human indi-

viduals. In the hypophysis of rats inoculated with the Walker rat tumor, McEuen and Selye<sup>7,8</sup> observed the appearance of large cells with eccentric nuclei and a granular chromophobe cytoplasm. Some of these cells contain vacuoles of unusual size. Guyer and Claus<sup>9,10</sup> noted similar histologic changes in the hypophysis of rats bearing the Flexner-Jobling carcinoma and regarded them as identical with those produced by castration. However, we<sup>16</sup> were able to produce similar changes by the intraperitoneal implantation of kidney tissue and concluded that "the changes produced by transplantable tumors are not necessarily related to the malignant growth as such but are at least partly due to decomposition of tissue in the necrotic centers of the tumor." Brown and Pearce<sup>17</sup> noted a slight hypertrophy of the hypophysis in rabbits inoculated with tumor tissue. Hammett<sup>18</sup> reported an insignificant increase in the size of the hypophysis in a rat bearing a "myxocavernous" type of hemangioma which occurred spontaneously in the peritoneum. Mendeléeff<sup>19,21</sup> claimed that normal guinea pig pituitary tissue increases the coagulability of plasma in vitro while the hypophysis of cancer-bearing guinea pigs is not very active in this respect.

In conclusion it may be said that both the spontaneously occurring tumors of man and the experimental growth of animals frequently produce definite morphologic changes in the anterior lobe, but it remains doubtful whether these should be regarded as specific effects of the tumor as such or merely as a result of toxic metabolites elaborated by the abnormal growths.

The author is greatly indebted to the International Cancer Research Foundation for subsidizing many of the investigations mentioned here which were performed in his laboratory.

#### REFERENCES

1. Albert, S., and Selye, H.: The Effect of Various Pharmacological Agents on the Morphogenetic Actions of Estradiol, *J. Pharmacol. & Exper. Therap.* 75: 308, 1942.
2. Baker, L. E., and Carrol, A.: Effect of Liver and Pituitary Digests on the Proliferation of Sarcomatous Fibroblasts of the Rat, *J. Exper. Med.* 47: 371, 1928.
3. Ball, H. A., and Samuels, L. T.: The Relation of the Hypophysis to the Growth of Malignant Tumors. III. The Effect of Hypophysectomy on Autogenous Tumors, *Am. J. Cancer* 26: 547, 1936.
4. Ball, H. A., Samuels, L. T., and Simpson, W.: The Relation of the Hypophysis to the Growth of Malignant Tumors. I. The Effect of Hypophysectomy on Transplanted Mammary Carcinoma in the White Rat, *Am. J. Cancer* 16: 351, 1932.
5. Ball, H. A., Schott, H. F., and Samuels, L. T.: Glycogen in Walker Tumor 256, *Cancer Research* 2: 146, 1942.
6. Baroni, V., Comsia, O., and Baroni, E.: Versuche über das Verhältnis zwischen einigen endokrinen Drüsen und Tumortransplantaten, *Endocrin. Ginec. si Obstetr.* 3: 131, 1938.
7. Berblinger, W.: Über experimentell hervorgerufene Hypophysilveränderungen, *Zentralbl. f. Path.* 25: 184, 1914.
8. Berblinger, W., and Muth, K.: Das histologische Bild der Adenohypophyse bei Krebs- und Sarkomleidenden im Vergleich zur Schwangerschaftshypophyse, *Zentralbl. f. Gynäk.* 47: 1923.
9. Bischoff, F., and Long, M. L.: Endocrine Factors Influencing Tumor Development. The Effect of Prolan Upon the Marsh-Buffalo Adenocarcinoma, *Endocrinology* 23: 327, 1938.

adrenotropic, mammotropic, lactogenic and, perhaps, also diabetogenic factors. On the other hand, judged by the inhibition of somatic growth and the atrophy of the thyroid and gonads, they appear to discharge subnormal amounts of growth-promoting thyrotropic and gonadotropic principles. Especially the inhibition of somatic growth is rather different from the manifestations of hyperactive anterior lobe tumors in man. Yet, even in human pathology the functional manifestations differ depending upon the type of tumorous growth, and the resemblance between these experimental tumors and the spontaneous anterior lobe adenomas of man is sufficiently great to make experimental work concerning inhibition of the rat tumors appear to be of some possible clinical applicability. From this point of view the activity of cistosterone and its esters is of special interest because these compounds appear to exert a pronounced antitumorigenic action uncontaminated by any significant degree of undesirable hormonal side-effects.

#### MORPHOLOGIC CHANGES IN THE ANTERIOR LOBE ELICITED BY EXPERIMENTAL TUMORS

Before discussing the experimental literature it may be well, for the sake of comparison, to survey briefly the data concerning hypophyseal changes in tumor-bearing patients.

Tumors of various organs may influence the structure of the pituitary gland. Thus in patients suffering from carcinomas, Karlefors<sup>53</sup> noted a decrease in the eosinophiles and an increase in the main cells. Krieger<sup>59</sup> found that the average weight of the gland is relatively high in cases of malignant tumors. Berblinger and Muth<sup>8</sup> noted an increase in main cells in cases of carcinoma or sarcoma, but they did not consider this to be a specific change and looked upon it merely as the effect of toxic products liberated from the tumor tissue. Saenger<sup>96</sup> observed a tumorlike proliferation of the main cells in the hypophysis of a woman with a large ovarian carcinoma. It seems questionable, however, whether this change should be attributed to the tumor as such, because the patient showed other signs of endocrine disturbances. Puccinelli<sup>90</sup> emphasized the occurrence of large quantities of pigment in the posterior lobe of tumor-bearing individuals. Kraus and Traube<sup>57</sup> state that in carcinoma-cachexia the number of basophiles is usually subnormal. Meessen<sup>79</sup> claimed that in carcinomatous patients, there is increased basophilic invasion in the posterior lobe.

Chorion epitheliomas in man occupy a particular position in so far as they produce gonadotropic hormones. Zondek<sup>118</sup> was the first to note that in such cases the pituitary shows pregnancy changes, a fact which has been confirmed by Erdheim<sup>30</sup> and Siegmund.<sup>108</sup>

With regard to experimental tumors the following observations are noteworthy. Berblinger<sup>7</sup> and Berblinger and Muth<sup>8</sup> showed that treatment with various protein extracts may lead to such changes in the rabbit pituitary as have been seen in carcinoma-bearing human indi-

37. Guyer, M. P., and Claus, P. E.: Cell Changes in the Anterior Lobe of the Pituitary Following Cancer Transplantation in Rats, *Anat. Rec.* 52: 225, 1932.
38. Guyer, M. P., and Claus, P. E.: Cellular Constituents of the Anterior Hypophysis After Uterine Implants of Carcinoma in Rats, *Anat. Rec.* 56: 373, 1933.
39. Guyot: Fibro-sarcoma du testicule gauche; castration; guérison, *Arch. méd. belges* 38: 159, 1890.
40. Guyot, J.: Un cas d'orchite goutteuse, *Bull. et mém. Soc. méd. d. hôp. de Paris* 2: 9, 1885.
41. Guyot, J., Creyx, M., Villar, J., Massiere, R., and Moretti, G.: Asthme et maladie de Basedow thyroïdectomie doublement curatrice, *Presse méd.* 47: 203, 1939.
42. Haagensen, C. D., Randall, H. T., and Auchincloss, R.: Failure of Thyrotropic Pituitary Hormone to Prevent Spontaneous Mammary Cancer in Mice, *Proc. Soc. Exper. Biol. & Med.* 45: 820, 1940.
43. Hammett, F. S.: Changes in the Endocrine Glands of a Tumor Bearing Female Albino Rat, *Endocrinology* 5: 216, 1921.
44. Hayashi, T.: The Relation Between the Hypophysis and the Growth of the Tumor, *Trans. Japanese Path. Soc.* 20: 661, 1930.
45. Heiman, J.: Growth of Transplanted Mammary Fibroadenoma in Castrated Rats Injected With Hormones, *Am. J. Cancer* 39: 172, 1940.
46. Hofbauer, J.: Stimulating Influence of the Anterior Pituitary Upon the Squamous Epithelium of the Cervix Uteri, *Proc. Soc. Exper. Biol. & Med.* 27: 1011, 1930.
47. Hofbauer, J.: Über Beziehungen des Hypophysenvorderlappens zum Uteruscarcinom, *Klin. Wchnschr.* 9: 2108, 1930.
48. Hofbauer, J.: Über Beziehungen des Hypophysenvorderlappens zum Uteruscarcinom, *Klin. Wchnschr.* 9: 2153, 1930.
49. Houston, S. W., and Miller, J.: The Action of Posterior Pituitary Extract in Controlling the Growth of Malignant Tumours, *Tr. Roy. Soc. Canada* 26: 71, 1932.
50. Howard, N. J.: Comparative Studies of Gonadotropic Hormones. V. Growth Response of Rat Mammary Glands in Chronic Experiments, *Proc. Soc. Exper. Biol. & Med.* 34: 732, 1936.
51. Hübscher, K.: Die biologische Hyperämiebehandlung von Adnexentzündungen mit Hypophysenvorderlappenhormon, *Zentrabl. f. Gynäk.* 57: 1575, 1933.
52. Julius, H. W.: The Action of the Gonadotropic Extract of Urine, Pregnyl on Tar Carcinoma, *Acta brev. Neerland.* 4: 74, 1934.
53. Karlefors, J.: Ueber Hypophyse und Thyreoiden bei Krebskranken, *Ztschr. f. Krebsforsch.* 17: 195, 1920.
54. Katz, K.: Hypophysenvorderlappen und Krebs, *Ztschr. f. Krebsforsch.* 45: 139, 1936.
55. Korteweg, R., and Thomas, F.: Tumorbildung und Tumorwachstum bei hypophysektomierten Mäusen, Paris, 1937, Leewenhoekvereniging, Vieme Conf.
56. Korteweg, R., and Thomas, F.: Tumor Induction and Tumor Growth in Hypophysectomized Mice, *Am. J. Cancer* 37: 36, 1939.
57. Kraus, E. J., and Traube, O.: Ueber die Bedeutung der basophilen Zellen der menschlichen Hypophyse, *Virchows Arch. f. path. Anat.* 268: 315, 1928.
58. Krehbiel, O. F., Haagensen, C. D., and Platenga, H.: "The Effect of the Anterior Pituitary Hormones on the Growth of Mouse Sarcoma, *Am. J. Cancer* 21: 346, 1934.
59. Krieger, M.: Ueber die Atrophie der menschlichen Organe bei Inanition, *Z. f. angew. Anat. u. Konstitutionslehre* 7: 87, 1920.
60. Lacassagne, A.: The Relation Between Hormones and Cancer, *Canad. M. A. J.* 37: 112, 1937.
61. Lacassagne, A.: Essai d'une hormone thyroïdrique en vue de modifier l'apparition de l'adrénocarcinome mammaire chez la souris, *Compt. rend. Soc. de biol.* 130: 591, 1939.
62. Lacassagne, A., and Nyka, W.: Indifférence du cancer greffé a la destruction de l'hypophyse chez le lapin, *Compt. rend. Soc. de biol.* 122: 747, 1936.
63. Lambadarides, A.: Einige biologische Ergebnisse aus der Röntgenbestrahlung der Hypophyse, *Strahlentherapie* 56: 273, 1936.
64. Loeb, L., Burns, E. L., Sontzeff, V., and Moskop, M.: Sex Hormones and Their Relation to Tumors, *Am. J. Cancer* 30: 47, 1937.

65. Loeb, L., and Kirtz, M. M.: The Effects of Transplants of Anterior Lobes of the Hypophysis on the Growth of the Mammary Gland and on the Development of Mammary Gland Carcinoma in Various Strains of Mice, *Am. J. Cancer* 36: 56, 1939.
66. Lustig, B., and Wachtel, H.: Versuch einer Methodik zur Pruefung von Substanzen auf ihre Eignung fuer die Chemotherapie des Carcinoms. II. Mitt. Vitamine, Hormone und Blutgerinnung beeinflussende Substanzen, *Biochem. Ztschr.* 71: 357, 1934.
67. Magath, M. A., and Lebenson, E.: Der Mechanismus der Prolanwirkung. Wirkung des Prolans auf den Kohlehydratstoffwechsel der Geschwülste in Gewebekulturen, *Vopr. Onkol.* 7: 217, 1935.
68. Magath, M. A., and Smoilowskaia, E. J.: Der Einfluss von grossen Dosen Prolan auf das Wachstum der überpflanzten Tumoren, *Vopr. Onkol.* 7: 225, 1935.
69. Marie, P., and Aubertin, Ch.: Cancer de l'utérus chez une lapine de neuf ans, *Bull. Assoc. frang. p. l'étude du cancer* 4: 253, 1911.
70. Maxwell, L. C., and Bischoff, F.: Studies in Cancer Chemotherapy. XI. The Effect of CO, HCN, and Pituitrin Upon Tumor Growth, *J. Pharmacol. & Exper. Therap.* 49: 270, 1933.
71. Mazer, C., Israel, S. L., and Alpers, B. J.: The Time Element in the Pituitary-Ovarian Response to Large Doses of the Estrogenic Hormone, *Endocrinology* 20: 753, 1936.
72. McEuen, C. S.: Effect of Hypophysectomy on Growth of the Walker Rat Tumor, *Proc. Soc. Exper. Biol. & Med.* 30: 928, 1933.
73. McEuen, C. S., and Selye, H.: Histological Changes in the Hypophysis and the Suprarenals of Rats Bearing Walker Rat Tumours, *Royal Society of Canada, Quebec Meeting*, 1934.
74. McEuen, C. S., Selye, H., and Collip, J. B.: Some Effects of Prolonged Administration of Oestrin in Rats, *Lancet* 230: 775, 1936.
75. McEuen, C. S., Selye, H., and Collip, J. B.: A Pigmented Adenoma of the Intermediate Lobe in a Rat Chronically Treated With Oestrin, *Proc. Soc. Exper. Biol. & Med.* 40: 241, 1939.
76. McEuen, C. S., Selye, H., and Thomson, D. L.: The Effect of Malignant Tumours on the Hypophysis, *Brit. J. Exper. Path.* 15: 221, 1934.
77. McEuen, C. S., and Thomson, D. L.: The Effect of Hypophysectomy on the Growth of the Walker Rat Tumour, *Brit. J. Exper. Path.* 14: 384, 1933.
78. McQueen-Williams, M., and Thompson, K. W.: The Effect of Ablation of the Hypophysis Upon the Weight of the Kidney of the Rat, *Yale J. Biol. & Med.* 12: 531, 1940.
79. Meessen, H.: Zur pathologie der Hypophyse, *Beitr. z. path. Anat. u. z. allg. Path.* 95: 39, 1935.
80. Mendeléeff, P.: Hypophyse et changements neuro-humoraux de cobayes cancéreux, *Compt. rend. Soc. de biol.* 119: 553, 1935.
81. Mendeléeff, P.: Recherches sur l'action hormonale de l'hypophyse au cours de l'évolution locale de la tumeur, *Cancer* 12: 287, 1936.
82. Möller, H.: Die Beziehungen zwischen Hypophysenvorderlappenhormon und Tumorwachstum, *Frankfurt Ztschr. f. Path.* 45: 571, 1933.
83. Mori, S.: Geschwulst und innere Sekretion. Die endokrinopathische endokrinoneurotische Theorie der Geschwulstdisposition, *Tr. Soc. path. jap.* 25: 1, 1935.
84. Mori, S., and Nakamura, M.: A Summary Observation About the Relation Between the Function of Internal Secretion and the Growth and Generation of the Tumor, *Tr. Soc. path. jap.* 20: 679, 1930.
85. Narimatsu, K.: An Experimental Study of the Effect of Pituitary Hormones on the Growth and Radiosensitivity of Malignant Tumor, Pt. I, *Jap. J. Obst. & Gynec.* 20: 387, 1937.
86. Nelson, W. O.: The Occurrence of Hypophyseal Tumors in Rats Under Treatment With Diethylstilbestrol, *Proceedings of the American Physiologic Society, Chicago Meeting*, 1941.
87. Noble, R. L., McEuen, C. S., and Collip, J. B.: Mammary Tumours Produced in Rats by the Action of Oestron Tablets, *Canad. M. A. J.* 42: 413, 1940.
88. Pierson, H.: Experimentelle Erzeugung von Uterusgeschwülsten bei Kaninchen durch Prolan, *Ztschr. f. Krebsforsch.* 45: 1, 1936.
89. Polson, R. J.: Anatomie und Pathologie der Spontanerkrankung der kleinen Laboratoriumstiere.
90. Puccinelli, E.: Sulle reazioni istochimiche di alcuni pigmenti del lobo posteriore dell'ipofisi, *Pathologica* 18: 311, 1926.

91. Reiss, M.: Ormoni si cresteren, *Rev. Endocrinol. Gynecol. Obstet.* 1: 271, 1936.
92. Reiss, M., Druckrey, H., and Hochwald, A.: Tumor und Inkretsystem, *Klin. Wchnschr.* 12: 1049, 1933.
93. Reiss, M., Druckrey, H., and Hochwald, A.: Beiträge zur hormonellen Steuerung des Tumorstwachstums und seines Stoffwechsels, *Ztschr. f. d. ges. exper. Med.* 90: 408, 1933.
94. Robertson, T. B., and Burnett, Th.: The Influence of the Anterior Lobe of the Pituitary Body Upon the Growth of Carcinomata, *J. Exper. Med.* 21: 280, 1915.
95. Robertson, T. B., and Burnett, Th.: The Influence of Tethelin, and of Other Alcohol-Soluble Extractives From the Anterior Lobe of the Pituitary Body Upon the Growth of Carcinomata in Rats, *J. Exper. Med.* 23: 631, 1916.
96. Saenger: Demonstration im ärztlichen Verein in Hamburg 1916, *Deutsche. med. Wchnschr.* 1370, 1916.
97. Samuels, L. T., and Ball, H. A.: Hypophysectomy and Tumor Growth. A Supplementary Statement, *Am. J. Cancer* 23: 801, 1935.
98. Samuels, L. T., Ball, H. A., and Simpson, V.: The Relation of the Hypophysectomy to the Growth of Malignant Tumors. II. The Response of Hypophysectomized Rats to Inoculation With the Walker Transplantable Mammary Carcinoma, *Am. J. Cancer* 18: 380, 1933.
99. Sciensinski, K.: Über den Einfluss von Hypophysenvorderlappen- und Schilddrüsenextrakten auf die Entstehung und den Verlauf von Teergeschwülsten (Untersuchungen über die Teergeschwülste, VI.), *Bull. internat. Acad. polon. d. sc. et d. lett., Cl. méd.* 4: 225, 1931.
100. Seel, L.: Versuche über Beeinflussung des Wachstums des experimentellen Teerkrebses durch Extrakte von Drüsen mit innerer Sekretion. I. Teerkrebs und Hypophysenextrakt, *Ztschr. f. Krebsforsch.* 22: 1, 1924.
101. Selye, H.: Endocrine Interrelations During Pregnancy and Lactation, *Advances in Modern Biol.* 5: 641, 1936.
102. Selye, H.: Interactions Between Various Steroid Hormones, *Canad. M. A. J.* 42: 113, 1940.
103. Selye, H.: The Pharmacology of Steroid Hormones and Their Derivatives, *Rev. Canad. de Biol.* 1: 577, 1942.
104. Selye, H.: *Encyclopedia of Endocrinology*, Vol. I. Classified Index of the Steroid Hormones and their Derivatives, Montreal, 1943, A. W. Franks.
105. Selye, H., and Clarke, E.: Ovarian Function in Hypophysectomized Rats, *Am. J. Anat.* 88: 393, 1944.
106. Selye, H., Collip, J. B., and Thomson, D. L.: Effect of Oestrin on Ovaries and Adrenals, *Proc. Soc. Exper. Biol. & Med.* 32: 1377, 1935.
107. Selye, H., Mortimer, H., Thomson, D. L., and Collip, J. B.: Effect of Parathyroid Extract on the Bones of the Hypophysectomized Rat. A Histologic Study, *Arch. Path.* 18: 878, 1934.
108. Siegmund, H.: Pubertas Praecox als Folge chorionepitheliomatöser Wucherungen, *Arch. f. Gynäk.* 149: 498, 1932.
109. Stilling, H., and Beitzke, H.: Über Uterustumoren bei Kaninchen, *Virchows Arch. f. path. Anat.* 214: 358, 1913.
110. Sugiura, K., and Benedict, S. R.: The Influence of Hormones on the Growth of Carcinoma, Sarcoma and Melanoma in Animals, *Am. J. Cancer* 18: 583, 1933.
111. Vargas, L., Jr.: Experimental Fibroids in Hypophysectomized Female Guinea Pigs, *Cancer Research* 3: 309, 1943.
112. Vassiliadis, H.: Au sujet de l'existence des substances antitumorales dans la surrenale et l'hypophyse, *Compt. rend. Soc. de biol.* 115: 1241, 1934.
113. Wagner, G. A.: Ueber multiple Tumoren im Uterus des Kaninchen, *Centralbl. f. allg. Path. u. path. Anat.* 16: 131, 1905.
114. Walker, C., and Whittingham, H.: The Effect of General Contraction of the Peripheral Blood-vessels Upon Mouse Cancers, *Lancet* 184: 1010, 1913.
115. Wiesner, B. P., and Haddow, A.: Gonadotropic Hormones and Cancer, *Nature* 132: 97, 1933.
116. Winternitz, M. C., and Waters, L. L.: The Effect of Hypophysectomy on Compensatory Renal Hypertrophy in Dogs, *Yale J. Biol. & Med.* 12: 705, 1940.
117. Zeldenrust, J.: Hypophysenvorderlappenhormone und die Bildung des experimentellen Tiercarcinoms, *Acta brev. Neerland. Physiol.* 4: 182, 1935.

118. Zondek, B.: Die Hormone des Ovariums und des Hypophysenvorderlappens, Berlin, 1931, Julius Springer.
119. Zondek, B.: Tumour of the Pituitary Induced With Follicular Hormone, *Lancet* 230: 776, 1936.
120. Zondek, B.: Hypophyseal Tumors Induced by Estrogenic Hormone, *Am. J. Cancer* 33: 555, 1938.
121. Zondek, B.: Clinical and Experimental Investigations on the Genital Functions and Their Hormonal Regulation, Baltimore, 1941, Williams & Wilkins Co.
122. Zondek, H., Zondek, B., and Hartoch, W.: Prolan and Tumorstadium. Der hemmende Einfluss des Prolans auf das Impfcarcinom der weissen Maus, *Klin. Wchnschr.* 11: 1785, 1932.

# THE ENDOCRINE EFFECTS OF PITUITARY TUMORS

## A CLINICAL REVIEW

WILLIAM J. GERMAN, M.D., NEW HAVEN, CONN.

*(From the Department of Surgery and the Brain Tumor Registry,  
Yale University School of Medicine)*

THE early attempts<sup>21</sup> to unravel the anatomic complexities of the region overlying the sella turcica led Galen to apply the term plexus retiformis to these structures. Vesalius, in spite of misinterpretation of anatomic structures, was led to the prophetic statement: "Rete mirabile, in quo vitalis spiritus ad animalem preparantur." For over 100 years, the "wonderful net" retained its secrets, until the keen eyes and wits of Willis separated the net into its component parts, on the basis of comparative anatomic studies. Bridging a gap of almost 200 years into the future, Willis stated: "The ramification of the carotids into a reticulated plexus shows . . . that the blood . . . before it is let into the cerebrum takes some part of the superfluous serum of the pituitary gland and instils another part into the various shoots to be led back toward the heart."

The modern conception of internal secretion was supplied by the brilliant studies of Claude Bernard. In the light of present knowledge, it is somewhat paradoxical that the first demonstration of functional activity of the pituitary by Schäfer (1894), was confined to the posterior lobe (1898).

Clinical interest in the pituitary gland was aroused by Marie's<sup>22</sup> disclosure that the condition he termed acromegaly was usually accompanied by an hypophysial tumor. The allied condition of gigantism had been studied not infrequently, but even the discerning mind of John Hunter had failed to note the enlarged pituitary fossa of the Irish giant's skeleton that he so carefully prepared. In fact, the dust of another century accumulated in the enormous sella turcica before Arthur Keith peered in and grasped its significance. Cunningham previously noted the enlarged sella turcica in this skull by palpating through the foramen magnum. Although an instance of pituitary tumor was recorded as early as 1771 by Greding, the pathologic nature of these pituitary enlargements was not clearly appreciated until Benda (1900)<sup>10</sup>



118. Zondek, B.: Die Hormone des Ovariums und des Hypophysenvorderlappens, Berlin, 1931, Julius Springer.
119. Zondek, B.: Tumour of the Pituitary Induced With Follicular Hormone, *Lancet* 230: 776, 1936.
120. Zondek, B.: Hypophyseal Tumors Induced by Estrogenic Hormone, *Am. J. Cancer* 33: 555, 1938.
121. Zondek, B.: Clinical and Experimental Investigations on the Genital Functions and Their Hormonal Regulation, Baltimore, 1941, Williams & Wilkins Co.
122. Zondek, H., Zondek, B., and Hartoch, W.: Prolan and Tumorwachstum. Der hemmende Einfluss des Prolans auf das Impfcarcinom der weissen Maus, *Klin. Wchnschr.* 11: 1785, 1932.

BABINSKI, J. (1900,<sup>4</sup> Fig. 2).—A girl 17 years of age had symptoms of headache, failing vision, epileptiform seizures, adiposity, genital hypoplasia, amenorrhea, and papilledema; autopsy disclosed a large tumor of the pituitary. This tumor was described eight years earlier by Babinski's student, Orianoft (1892).<sup>5a</sup>

FRÖHLICH, A. (1901,<sup>7a</sup> Fig. 3).—A boy 14 years of age had symptoms of headache, visual impairment, vomiting, and rapid gain in weight; examination revealed unilateral amblyopia, temporal hemianopia, adiposity, feminine physique, genital dystrophy, scanty hair, and dry skin. This patient was operated upon by von Eiselsberg, in 1907, and a cystic tumor partially removed from the sella turcica; histologic diagnosis was carcinoma or, more probably, an adenoma of the hypophysis in the precancerous stage.



Fig. 2.—Babinski, hypopituitarism.

LORAIN, P. (1871).<sup>5a</sup>—A syndrome was described consisting of: (1) weakness, gracefulness, and smallness of the body, as an arrested development affecting the mass of the body; (2) persistent youthfulness; (3) feminine characteristics in males, as broad hips, feminine distribution and character of hair, genital hypoplasia, and development of the breasts.

LEVI, E. (1908,<sup>52</sup> Case 1, Fig. 4).—A girl 20½ years old had developmental arrest since the age of 10 years, headaches, vomiting, amenorrhea, progressive visual failure, optic atrophy, and radiographic enlargement of the sella turcica (nearly 2 cm.).

GILFORD, H. (1897,<sup>37</sup> Case 1, Fig. 5).—A boy 17 years old had arrest of body growth (height 3 feet 8½ inches, weight 35.2 pounds) and premature senility; infantilism and senilism were both present. He died at the age of 18 with small cirrhotic kidneys and atheroma of the coronary arteries. The name progeria was given to this condition by Gilford in 1904.<sup>38, 39</sup>



Fig. 3.—Fröhlich, Fröhlich syndrome.

SIMMONDS, M. (1914).<sup>78</sup>—A woman 46 years of age had puerperal sepsis eleven years previously, followed by amenorrhea, asthenia, vertigo, episodes of unconsciousness, emaciation, premature senility, and anemia. Autopsy revealed small abdominal organs, embolic necrosis of pituitary, noninflammatory.

CUNNINGHAM, D. J. (1891).<sup>18</sup>

KEITH, A. (1911,<sup>45</sup> Fig. 6).—The Irish giant, O'Brien (or Byrne), died in 1783 at the age of 22 years. The skeleton, which was obtained by John Hunter and is preserved in the Museum of the Royal College of Surgeons, London, has a stature of 7 feet, 8¾ inches; the sella turcica has an anteroposterior diameter of 21 mm., width 24 mm., depth 11 mm.

## THE PITUITARY ADENOMAS

Analyses of the symptoms observed in groups of patients with the various types of pituitary adenomas\* afford a logical starting point for the subject under consideration. The analyses will be limited to endo-

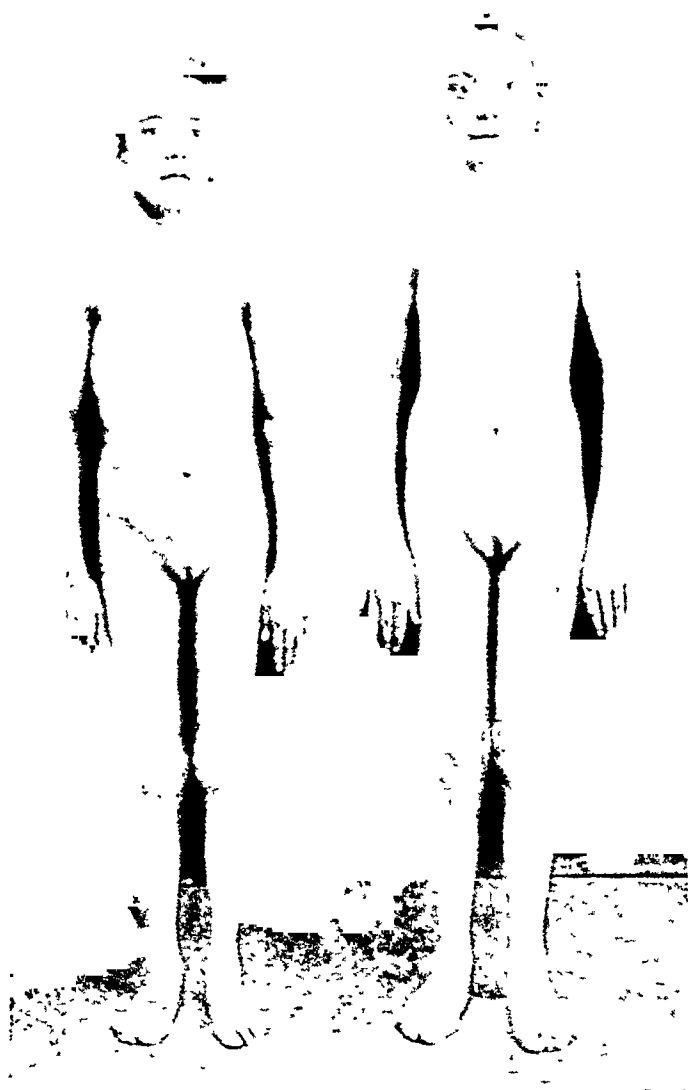


Fig. 4.—Levi, hypopituitarism, Lorain-Levi type. Left (Case 2), age 15 yr., 5 mo., right (Case 1, sister of patient in Case 2), age 20 yr., 6 mo.

crine symptomatology, although this forms only a portion of the total clinical picture. Both positive and negative phases of pituitary functions may be distinguished in these syndromes. Some of the negative

\*Craniopharyngiomas are omitted, since their endocrine picture appears to result from combined pituitary and hypothalamic disturbances.

TABLE I  
ACROMEGALY  
(DAVIDOFF, 100 CASES)

SYMPTOM	INCIDENCE (%)
Enlargement of acral parts ( <i>Gigantism</i> , 14)	100
Disturbance of menstrual cycle	87*
Complete amenorrhea	73*
Increased basal metabolic rate	70†
Excessive perspiration	60
Hypertrichosis	53
Cutaneous pigmentation	46
Gain in weight	39
Diminished libido sexualis	38
Asthenia	33
Low blood pressure (less than 120 mm. Hg systolic)	30
Polyphagia	28
Fibromata mollusca of skin	27
Polydipsia	25
Enlarged thyroid gland	25
Glycosuria ( <i>diabetes mellitus</i> , 12)	25
Decrease of body hair	7
Persistent lactation	4
Failure of breasts to develop	4

\*Percentage of female patients.

†Percentage of 70 cases examined.

excessive perspiration (60 per cent), gain in weight (39 per cent), and polyphagia (28 per cent) may be accounted for on the basis of excessive elaboration of the growth factor by the tumor. This tendency toward tissue overgrowth affects the viscera as well, in the form of splanchnomegaly (Cushing and Davidoff<sup>24</sup>). Of other prominent symptoms, disturbance of the menstrual cycle (87 per cent) is undoubtedly a gonadotropic effect and diminished libido (38 per cent) is probably in the same category. The symptoms of asthenia (33 per cent), low blood pressure (30 per cent), cutaneous pigmentation (46 per cent), polydipsia (25 per cent), glycosuria (25 per cent), and enlarged thyroid gland have been referred to as polyglandular effects.

*Chromophobe Adenomas.*—Chromophobe is the most common tumor of the pituitary, accounting for about 73 per cent of the adenomas. The clinical picture depends upon the age of the patient at the onset of tumor growth, pituitary dwarfism being observed in those patients in whom the tumor is well advanced before adolescence. The endocrine syndrome produced by the chromophobe adenoma is almost the complete antithesis of that due to the acidophile adenoma; it is characterized by hypopituitarism.

The chromophobe cells compose about 52 per cent of the cells of the normal adenohypophysis, according to Rasmussen.<sup>64</sup> These chromophobe mother cells of the normal gland are apparently identical with the cells of the chromophobe adenomas. Although these cells possess no cytologic characteristics of secreting cells, Severinghaus<sup>73</sup> has noted that they contain two distinctive types of Golgi bodies: a net type, characteristic of the acidophile cell, and a ring type, similar to that

of the basophile cell. Thus, the final secretory phase appears to be predetermined in the chromophobe mother cells. Applying this method of study to a few adenomas removed at operation by Cushing,<sup>23</sup> Severinghaus found: "(a) that in the adenoma of acromegaly the Golgi body of all cells, whether chromophobe or acidophilic, is of acidophilic type; (b) that in the chromophobe adenomas the cells with a Golgi body of acidophilic type far outnumber those with a Golgi body of basophilic type." Bailey and Cushing<sup>4</sup> had previously suggested, on the basis of staining characteristics, that "the chromophobe cells are not all of the same nature."

The endocrine effects of chromophobe adenomas are tabulated in Table II, based upon the records of 100 consecutive cases of Cushing's series in the Brain Tumor Registry, Yale University School of Medicine.\* The sex distribution was 53 males and 47 females. The age incidence was: second decade, 5; third decade, 14; fourth decade, 23; fifth decade, 33; sixth decade, 19; seventh decade, 5; eighth decade, 1. Since the presence or absence of certain symptoms were not specifically noted on all records, the percentage incidence of symptoms is calculated on the basis of the number of cases in which specific mention of the symptom was found, as well as the total number of cases.

Disturbance of the menstrual cycle occurred in 97 per cent of women between the ages of 15 and 45 inclusive, 94 per cent having amenor-

TABLE II  
CHROMOPHOBE ADENOMAS  
(100 CASES)

SYMPTOM	INCIDENCE (%)	
	WHERE NOTED	TOTAL
Disturbance of menstrual cycle	78	78*
Subnormal basal metabolic rate (below -5)	77	76
Abnormality of skin (fine, dry)	81	56
Abnormality of hair (distribution, fine, scant)	55	53
Gain in weight	51	47
Diminished libido sexualis	62	39
Subnormal blood pressure	40	39
Diminished potentio sexualis	71	28†
Subnormal temperature	33	23
Somnolence	31	22
Genital abnormality (hypoplasia)	33	15
Polydipsia (slight)	13	12
Mammary hypoplasia		11*
Questionable enlargement of acral parts	12	9
Weakness	10	9
Polyuria (slight)	10	9
Feminine habitus in males		8†
Small acral parts	7	5
Appetence for sweets (slight)	6	5
Small stature	6	3
Glycosuria (slight)	3	2

\*Percentage of female patients.

†Percentage of male patients.

\*With the kind assistance of Dr. Louise Eisenhardt.

rhea. Of the 15 women over 45 years of age, 40 per cent had amenorrhea before the age of 45. Diminished libido sexualis occurred in 39 per cent of all patients but was noted in 62 per cent\* of those whose records contained a specific note concerning it. It was lost in 30 per cent and diminished in 32 per cent. Diminished potentio sexualis was recorded in 28 per cent of all male patients, but in 71 per cent\* of those where this symptom was specifically noted. It was lost in 42 per cent and diminished in 29 per cent. In those patients whose genital status was noted, hypoplasia or atrophy was present in 22 per cent and genital infantilism in 11 per cent. Mammary hypoplasia was found in 11 per cent of the female patients while one male exhibited enlargement of the breasts. Feminine habitus appeared in 8 per cent of the males while feminine distribution of the hair was noted in 19 per cent. It is obvious that sexual functions are severely disturbed by the growth of a chromophobe adenoma. Evidence that this disturbance is due to compression of the normal basophilic elements by the expanding adenoma has been presented by Cushing<sup>23</sup> and will be discussed later.

Another group of symptoms is not greatly different from those observed in hypothyroidism. Basal metabolic rates of less than  $-5$  were found in 76 per cent of all cases. Of these, 24 per cent were  $-6$  to  $-15$ , and 39 per cent were  $-16$  to  $-25$ , while 15 per cent were below  $-25$ . There were 20 per cent in the normal range of  $-5$  to  $+5$ , and 3 per cent were  $+5$  to  $+10$ . The skin was noted to be abnormal (fine, dry) in 56 per cent of all patients. Of these, 46 had fine skin; the skin was unusually dry in 25 and finely wrinkled in 7. Only 2 patients had coarse skin, and excessive perspiration was present in 2. Gain in weight was recorded in 47 per cent of all cases, being only a slight increase in 23 patients but frank obesity was present in 24. Weight loss occurred in 5 cases while 2 patients exhibiting pituitary dwarfism had subnormal weights. Subnormal temperature was found in 23 per cent of all patients and somnolence was noted in 22 cases. It would be tempting to ascribe this group of symptoms to a deficiency in the thyrotropic hormone of the adenohypophysis. However, since the elevated basal metabolism frequently observed in acromegaly responds poorly to thyroidectomy, it appears likely that the pituitary itself is partially responsible. Another bit of evidence in this respect is found in the condition of the hair in patients with chromophobe adenomas. The hair was scant in 47 cases, but this was usually limited to the body hair. Fine hair was noted in 19 patients, while only 2 had coarse hair. Feminine distribution of the hair has already been mentioned in 19 per cent of male patients. This tendency toward feminine type of hair is corroborated by the fact that normal hair was noted in only 13 males as opposed to 28 females. Increased hair was mentioned in one case.

In view of the consistent elevation of blood pressure in cases of basophilic adenoma, it is interesting to note subnormal blood pressure

---

\*The actual incidence probably approximates the higher figures.

in 39 per cent of these patients with chromophobe adenomas. The range of "normal" blood pressure for various age groups has been established by the studies of Robinson<sup>40</sup> and The Life Extension Examiners.<sup>41</sup> In the present series, systolic hypotension occurred in the various age groups as follows: Second decade, 2 of 5 patients had systolic pressures under 100 mm.; third decade, 4 of 13 under 110 mm.; fourth decade, 13 of 22 under 115 mm.; fifth decade, 10 of 32 under 120 mm.; sixth decade, 9 of 19 under 120 mm.; seventh decade, 1 of 5 under 120 mm. Systolic hypertension over 150 mm. occurred in only 4 patients of the 97 whose blood pressure was recorded; systolic and diastolic (over 100 mm.) hypertension was present in 3 patients; all patients with hypertension were in age groups over 40. The average blood pressures for the various ages were as follows: second decade, 109/59; third decade, 111/71; fourth decade, 117/75; fifth decade, 124/80; sixth decade, 128/78; seventh decade, 154/83.

It was a little surprising to find questionable enlargement of acral parts mentioned in 9 per cent of the cases. Undoubtedly the various clinical observers were searching for such changes and it is probably significant that in no case was there unequivocal acral enlargement. However, perhaps this question should not be passed over so lightly since it has already been noted that chromophobe adenomas are composed of cells, the majority of which resemble the normal mother cell of the acidophilic type, on the basis of Golgi body characteristics. It is not impossible, therefore, that some of these cells might mature to the extent of elaborating some internal secretion. Such maturation probably occurs in the mixed adenomas soon to be discussed. The negative phase of acral overgrowth was observed in only 5 per cent of the patients, the same number who sought treatment during the second decade. Small stature was present in 3 per cent. These symptoms are undoubtedly dependent upon the onset of tumor growth before adult proportions have been attained. They are probably related to pressure atrophy of the acidophilic elements of the normal gland by the expanding adenoma within the confines of the sella turcica.

A few other symptoms are worthy of brief note at this time, on the basis of their possible relation to secondary disturbance of other endocrine glands. Possible effects upon the thyroid have already been mentioned. In regard to the pancreas, increased sugar tolerance, although not included in the table of symptoms, is observed, not infrequently, in cases of chromophobe adenoma and will be discussed later. However, symptoms suggestive of pancreatic deficiency were observed as follows: polydipsia 12 per cent, polyuria 9 per cent, increased appetite for sweets 5 per cent, and glycosuria 2 per cent. All these were slight or questionable in degree and it is not unlikely that they were due to pressure upon the hypothalamus. Inquiry was made, in most of the cases, concerning possible adrenal disturbance: subnormal blood pressure in



39 per cent has been mentioned; weakness was a complaint in 10 per cent but abnormal pigmentation of the skin was not observed.

*Simmonds's Disease.*—Since the endocrine syndrome of chromophobe adenomas is predominantly suggestive of hypopituitarism, the pure state of hypopituitarism as observed in Simmonds's disease is worthy of comparison. This condition is frequently the result of pituitary infarction from severe puerperal hemorrhage or sepsis. Of the 42 cases reviewed by Silver,<sup>77</sup> 10 were due to tumor involving the pituitary as follows: complete destruction of hypophysis by basophilic adenoma, 2;\* carcinoma, 2; cyst, 5; "fibroblastic endothelioma of Masson," 1. It is perhaps significant that chromophobe adenoma was not an etiologic agent. The symptoms of Simmonds's disease are shown in Table III, on the basis of the review by Silver.<sup>77</sup>

TABLE III  
SIMMONDS'S DISEASE  
(SILVER, 42 CASES)

SYMPTOM	INCIDENCE (%)
Cachexia	100
Loss of pubic hair	86
Loss of axillary hair	79
Asthenia	64
Genital atrophy	60†
Amenorrhea	55*
Loss of teeth	36
Progeria	29
Atrophy of jaw	24
Hypothermia	21
Loss of libido	14
Eosinophilia	14
Anemia	14
Hypotension	7

\*Percentage of female patients, age 15 to 45 at onset.

†Percentage of male patients.

The most striking disparity between the hypopituitarism of Simmonds's disease and that caused by chromophobe adenomas is the appearance of cachexia in 100 per cent of the cases of Simmonds's disease while gain in weight was noted in 47 per cent of the chromophobe adenoma patients and cachexia was not mentioned in any. Asthenia (64 per cent) in Simmonds's disease is probably related, at least in part, to the cachexia. Abnormality of hair is not dissimilar in the two conditions, but loss of teeth in 36 per cent of the cases of Simmonds's disease is striking in the absence of such change in patients with chromophobe adenomas. Similarly, progeria, noted in 29 per cent of the patients with Simmonds's disease, was absent in the chromophobe adenoma cases. In fact, chromophobe adenomas sometimes seem to have a reverse effect, giving an appearance younger than the actual age (ateleiosis).<sup>46</sup> There is no obvious explanation for the higher incidence

\*From the pathologic description of these tumors, it is not unlikely that they were chromophobe adenomas.

of amenorrhea and loss of libido in patients with chromophobe adenoma.

At present there is insufficient ground for more than speculation on the difference in the hypopituitary picture produced by these two conditions. Although certain cases of Simmonds's disease, especially those due to pituitary thrombosis, are characterized by a rapid course, the presence of this syndrome due to tumors causing hypophyseal destruction makes it unlikely that the time factor is of great importance. It appears improbable that the cause of this difference is to be found in the posterior lobe, since the neurohypophysis was reported to be normal in 60 per cent of the cases of Simmonds's disease reviewed by Silver.<sup>7</sup> It is possible that the adenohypophysis is less affected by the pressure of an expanding chromophobe adenoma than it is in Simmonds's disease, even when the latter is due to tumor. However, it is difficult to understand how a significant amount of normal adenohypophysis could be preserved in the presence of a huge, sella-expanding adenoma. Even so, one would expect the difference in the syndrome to be one of degree rather than of kind. It is true that the weight gain, so characteristic of patients with chromophobe adenoma, might be hypothalamic in origin. However, obesity often occurs in the absence of any other signs of hypothalamic disturbance. There remains the possibility that the difference under discussion may be due to the actual elaboration of a hormone by the supposedly functionless cells of the chromophobe adenoma. To date there is no positive evidence for this.

*Mixed Adenomas.*—In 1910, Cushing<sup>19</sup> stated: “. . . in many of the cases in which existing hypopituitarism is the striking feature traces at least of an early tendency to hyperpituitarism can be detected.” Dott and Bailey,<sup>27</sup> on the basis of a study of hypophyseal adenomas from Cushing's Clinic, found 13 examples of mixed adenomas in which “the features of acromegaly and of the hypopituitary syndrome develop synchronously rather than in sequence.” In 1928, Bailey and Cushing<sup>8</sup> reported the results of further studies on this acromegalic type of hypopituitarism and applied to it the term fugitive acromegaly. This syndrome was identified in 22 instances of 100 adenomas studied. A method of differential staining was applied to these tissues, using neutral ethyl-violet and orange G, for the identification of alpha granules.<sup>7</sup> The symptoms of fugitive acromegaly are shown in Table IV, based on 22 cases of Bailey and Cushing.<sup>8</sup> Aside from the symptoms noted in this table, the syndrome of the mixed adenomas is similar to that of the chromophobe adenomas.

The symptoms noted in Table IV are usually mild in degree and the clinical picture is generally more suggestive of hypopituitarism than the reverse. In fact, most of the cases in Bailey and Cushing's<sup>8</sup> series were originally classified as chromophobe adenomas. The symptoms of

TABLE IV  
MIXED ADENOMAS  
(BAILEY AND CUSHING, 22 CASES)

SYMPTOM	INCIDENCE (%)
Coarsening of features	36
Enlargement of hands and feet	27
Excessive height	23
Squaring or tufting of phalanges	23
Normal or slightly elevated basal metabolic rate	18
Hypertrichosis	14
Normal or exaggerated libido	14
Excessive perspiration	9
Persistent lactation	5
Glycosuria	5
Spacing of teeth	5

hyperpituitarism are best described as traces of acromegaly, using the term acromegaly in a broad sense, covering the entire syndrome rather than merely the acral manifestations. The microscopic picture is likewise characterized by relatively scant evidence of acidophilic cellular activity, fine alpha granules usually appearing as a ring in the peripheral cytoplasm. It remains a matter of speculation whether these adenomas represent: differentiation within a chromophobe adenoma, de-differentiation within an acidophilic adenoma, or a specific mixed adenoma from beginning to end. Bailey and Cushing<sup>8</sup> inclined toward the last hypothesis, suggesting that the alpha cells remain of embryonic type.

*Basophilic Adenomas.*—Two examples of basophilic adenoma were described by Erdheim,<sup>30</sup> in 1903. In his monograph on *The Pituitary Body and Its Disorders*, published in 1912, Cushing described a case showing a "syndrome of painful obesity, hypertrichosis, and amenorrhea with overdevelopment of secondary sexual characteristics." In the light of present knowledge, this patient probably had a basophilic adenoma of the pituitary.<sup>21</sup> Several similar cases were reported by various authors during the ensuing years but pathologic verification of a basophilic adenoma in a patient with the syndrome of plethoric obesity, amenorrhea, purpuric ecchymoses and cutaneous striae, facial hirsutes, exophthalmos, and vascular hypertension was first reported by Parkes Weber<sup>33</sup> in 1926. However, it was not until several years later (Teel<sup>39</sup>) that the significance of the small basophilic adenoma was appreciated. Our present knowledge of the syndrome of "pituitary basophilism" is chiefly due to the work of Cushing,<sup>22</sup> whose contributions to the subject have been so extensive that the eponym—Cushing's disease—sometimes applied to the condition, is not inappropriate.

The symptoms produced by basophilic adenomas are tabulated in Table V, based upon the review of 47 verified cases from the literature and from Cushing's Clinic, by Eisenhardt and Thompson.<sup>28</sup> The characteristic appearance of these patients includes: round, plethoric face; obesity, sparing the extremities; round shoulders or kyphosis; cutaneous

striae, principally of the lower abdomen; female hirsutism. Since the presence or absence of certain symptoms was not specified in some of the case reports, percentages are calculated on the basis of the number of cases in which specific mention of the symptom was found, as well as the total number of cases.

TABLE V  
BASOPHILIC ADENOMAS  
(EISENHARDT AND THOMPSON, 47 CASES)

SYMPTOM	INCIDENCE (%)	
	WHERE NOTED	TOTAL
Characteristic appearance	98	96
Amenorrhea	81*	81*
Irregular or scanty menses	16*	16*
Impotentia	92†	92†
Skeletal decalcification	95	85
Blood pressure elevation (above 150 systolic or 100 diastolic)	90	81
Glycosuria or decreased sugar tolerance	70	55
Erythrocytosis	52	36
Exophthalmos	85	23
Elevated basal metabolic rate (above +15)	25	15
Decreased basal metabolic rate (below -15)	25	15

\*Percentage of female patients with pelvic organs present.

†Percentage of adult male patients.

The syndrome of pituitary basophilism was found by Crooke<sup>17</sup> in 12 patients whose pituitary glands showed merely a hyaline change in the basophiles. This finding was confirmed by Rasmussen<sup>65</sup> in 3 additional cases. Conversely, Susman<sup>68</sup> reported eight instances of basophilic adenoma without evidence of Cushing's syndrome. Finally, a similar syndrome may occur as the result of hyperadrenalism<sup>12, 47</sup> or thymic tumor.<sup>53</sup> In spite of this apparent conflicting evidence, it appears certain that the syndrome described by Cushing is most frequently related to pathologic changes in the basophiles of the pituitary gland. In fact, Crooke<sup>17</sup> found that the characteristic hyaline change of the cytoplasm of the basophiles of the anterior lobe of the pituitary was present in all clinical examples of the syndrome, whether associated with pituitary, adrenal, or thymic tumor or in the absence of any endocrine adenoma. It is of interest that this hyaline change does not appear in the cells composing a basophile adenoma but is found in the basophiles of the adjacent anterior lobe. The recent article by Thompson and Eisenhardt<sup>90</sup> confirms Crooke's findings (Table VI). The physiologic significance of the Crooke changes is subject to two interpretations: (1) an expression of altered physiologic activity (Crooke); (2) a degenerative change following a period of physiologic overactivity of the basophiles (Severinghaus and Thompson<sup>76</sup>).

In spite of the extensive experimental and clinical work upon the physiology and pharmacology of the pituitary body, critically digested by Van Dyke<sup>92</sup> on two occasions, sufficient definitive data are not yet

TABLE VI  
VERIFIED CASES OF CUSHING SYNDROME TO 1940  
(THOMPSON AND EISENHARDT)

ASSOCIATION WITH TUMOR	TOTAL NO. OF CASES	PERSONAL EXAMINATION OF PITUITARY	
		NO. OF CASES	NO. OF CASES WITH CROOKE CHANGE
Pituitary adenoma*	60	39	35
Adrenal tumor	22	11	11
Thymic tumor	3	3	3
Arrhenoblastoma	1	1	1
No tumor of any gland	12	9	8
Total	98	63	58

\*Of the 60 pituitary adenomas, 49 were reported as basophilic.

available to allow interpretation of the component parts of the syndrome of pituitary basophilism. Identification of the basophiles with a gonadotropic function of the anterior pituitary was suggested by Addison's<sup>1</sup> observation of vacuolization of basophiles following castration in the rat.\* Confirmation was added by Engle's<sup>20</sup> discovery of increased gonadotrophic potency of pituitary glands obtained from castrated rats. Smith's<sup>80</sup> demonstration of greater sex-maturing potency in the basophile-rich central core of the bovine anterior lobe, compared with that of the acidophile-rich rind, supplied further evidence. However, the direct application of these experimental data to the syndrome of basophilism is confusing in view of apparent diminution of sex functions in clinical cases.† The appearance of a similar syndrome in certain patients with adrenal tumor suggests that parts of the clinical picture may be mediated through the adrenal glands. In fact, hypertrophy of the adrenal cortex, especially the zona fascicularis, has been a striking feature in most instances of basophilism. Other portions of this confusing clinical syndrome will be discussed later.

#### POST-MORTEM FINDINGS

*Acidophilic Adenomas.*—Additional data concerning the endocrine effects of pituitary tumors have been obtained from post-mortem studies. In spite of numerous individual case reports, there are surprisingly few studies based upon a significant number of cases. A striking exception is found in the monograph on acromegaly by Atkinson,<sup>5</sup> containing analysis of 265 post-mortem examinations. Unfortunately, the source material was apparently not suitable for statistical purposes, although data such as the following occasionally appear: The thyroid in 141 cases of acromegaly was hypertrophied in 57 per cent, cystic in 19 per cent, normal in 16.3 per cent, and atrophied in 7 per cent; the

\*Basophilic castration cells do not appear in the guinea pig (Severinghaus).<sup>74</sup> In man, the situation is confusing (Kon<sup>75</sup> and Rössle<sup>76</sup>), in fact some reports (Philipp<sup>73</sup>) suggest that the castration effects may appear in the acidophiles.

†Precocious adolescence, at 10 years of age, was present in Cushing's<sup>22</sup> case (A. D.), but this was followed by amenorrhea three years later.

thymus in 98 cases was persistent in 54.6 per cent. Other endocrine organs are mentioned as follows: The pancreas has been described as indurated, enlarged, normal, or showing islet atrophy; the adrenals have been described as normal, atrophied, enlarged, or containing cortical adenomas; the parathyroids are occasionally enlarged; the ovaries have been described as cystic, fibrotic, sclerosed, or degenerated.

In order to obtain more informative data on the post-mortem findings in acromegaly, from the endocrine aspect Table VII was compiled from the studies of Cushing and Davidoff<sup>24</sup> and of Goldberg and Lissner.<sup>40</sup>

These post-mortem findings serve to emphasize certain specific effects of acidophilic adenoma of the pituitary upon the other endocrine organs. The diverse endocrine changes appear to indicate that these effects are not merely an expression of general organomegaly, although enlargement of organs is as much a characteristic of the disease as is skeletal overgrowth. Examples of the enormous size which may be attained by organs of acromegalies are a liver of 6200 Gm. (Goldberg and Lissner<sup>40</sup>) and a heart weighing 1275 Gm. (Osborne<sup>60</sup>). The importance of cardiomegaly was emphasized by Courville and Mason,<sup>16</sup> who reported evidence of marked heart failure in 75 per cent of 24 patients with acromegaly, 6 of whom died of heart failure with cardiomegaly.

*Thyroid.*—Of all the endocrine organs aside from the pituitary itself, more data are available on the thyroid gland in acromegaly. The analysis of Atkinson<sup>5</sup> has already been mentioned. The trend toward colloid or adenomatous enlargement of the thyroid, shown in Table VII, is confirmed by the studies of Davis<sup>26</sup> on the thyroid gland in 166 cases of acromegaly. The thyroid was enlarged in 52 per cent, with basal metabolic rate greater than +10. Thyroidectomy was done in 27 cases (5 deaths), 26 of the glands being adenomatous and 23 colloid in type; only 3 glands were hyperplastic. The reduction in basal metabolic rate after thyroidectomy was less constant and less in degree than in hyperthyroidism without acromegaly. Concerning the thyroid enlargement in acromegaly, Cushing and Davidoff<sup>24</sup> stated: “. . . out of 45 cases which we have tabulated, the gland was below normal weight only in . . . 2 cases . . . ; whereas it was said to have been ‘large’ or ‘very large’ in 11 cases; and in the other 29 in which the weights were given the average was 129 Gm. The largest recorded thyroid was in Geddes’ case (1909)<sup>36</sup> of 312 Gm. . . .”

*Parathyroids.*—There are very few reports on the state of the parathyroids in acromegaly. These glands were mentioned in 3 of the 8 cases summarized in Table VII, being normal, large, and adenomatous, respectively. The “normal” gland was reported as showing a suggestion of proliferative activity. Slight enlargement of the parathyroids was described by Reinhardt and Creutzfeldt,<sup>66</sup> and Bartlett.<sup>9</sup> A parathyroid adenoma was recorded by Josefson.<sup>44</sup> On the basis of present information it is possible only to state that the parathyroids *may* be

TABLE VII  
POST-MORTEM FINDINGS IN ACROMEGALY

CASE	SEX	AGE	DIABETES	SPLANCHNO-MEGALY	THYROID LARGE	PARATHYROID	THYMUS LARGE	ADRENALS LARGE	PANCREAS	GONAD ATROPHY	CAUSE OF DEATH
<b>Cushing and Davidoff</b>											
1	M	52	-	+	Colloid, adenomas	Slight hyperplasia	+	Cortical adenomas	Large, few islets	-	Cardiovascular
2	M	40	-	+	Colloid	-	-	+	Normal islets	+ Few Leydig cells	Operative fatality
3	M	35	±	-	Colloid adenoma	Adenomas	+	Cortical adenomas	Large, large islets	+ No Leydig cells	Cardiac failure
4	F	52	+	+	Colloid cysts	-	-	+	Normal	+	Diabetic coma
<b>Goldberg and Lissner</b>											
1	M	37	+	-	-	-	+	Cortical adenoma, hyperplastic medulla	-	-	Anesthesia— $\text{N}_2\text{O}-\text{O}_2$
2	M	45	-	+	Colloid	Large	+	Cortical adenomas and hyperplasia	-	-	Purulent sphenoiditis
3	F	58	+	-	Nodular	-	Normal	-	Few islets	+	Hemorrhage from pituitary adenoma
4	F	43	+	-	-	-	Medullary degeneration	-	-	+	Suicide

enlarged or adenomatous in acromegaly. It is hoped that future post-mortem reports will include the condition of these glands.

*Thymus.*—Enlargement of the thymus is a frequent finding in acromegaly; the reported persistence of the thymus in 54.6 per cent of 98 cases by Atkinson<sup>6</sup> has already been mentioned. The thymic enlargement was so striking in the case of Fritzsche and Klebs,<sup>23</sup> reported in 1884, that the thymus was thought to be the causative agent. Even Marie<sup>54</sup> was impressed by the thymic enlargement in acromegaly. The thymus was large in 4 of the 6 cases in Table VII in which its condition was recorded; the weight of the organ was 78 Gm. in Cushing and Davidoff's Case 3. The significance of the thymic enlargement in acromegaly is not clear, since similar enlargement may occur in the reverse state of hypopituitarism.

*Adrenals.*—Enlargement of the adrenals was noted in 6 of the 7 cases in Table VII in which their size was recorded. The greatest combined weight was 43 Gm. in Cushing and Davidoff's Case 2. Adrenals of combined weight of 57 Gm. were reported in an acromegalic by Schultze and Fischer.<sup>72</sup> Cortical adenomas were present in 6 of the 8 cases (Table VII). It is apparent that adrenal hypertrophy, often with cortical adenomas, is characteristic of acromegaly.

*Pancreas.*—Pancreatic enlargement was noted in 2 of 5 cases shown in Table VII, coinciding with Cushing and Davidoff's<sup>24</sup> calculation of an average weight of 143 Gm. in 14 case reports, analyzed by them. The heaviest pancreas weighed 250 Gm. (Launois and Roy<sup>51</sup>). It is not unlikely that pancreatic enlargement is merely one manifestation of acromegaly. The islands of Langerhans have been described as hypertrophic in some cases of acromegaly. This was true in 1 of 5 cases (Table VII); in the remaining cases the islets were normal in 2 and scanty in 2.

Clinical diabetes was present in 4 of the 8 cases and transient in a fifth case; 1 patient died in diabetic coma. The incidence of diabetes mellitus in 153 cases of acromegaly was found to be 17 per cent by Coggeshall and Root<sup>13</sup>; glycosuria was present in 36 per cent. These observers reported that diabetes was the direct or indirect cause of death in 7 of the 17 known dead among their 26 diabetic acromegalics.

*Gonads.*—Atrophy of the gonads was noted in 5 of 7 cases in Table VII. The microscopic findings in the testes were as follows: Case 1, normal spermatogenesis and great excess of the interstitial cells of Leydig; Case 2, atrophy with no formed spermatozoa and only a few scattered cells of Leydig; Case 3, advanced atrophy of the tubules with no differentiation of the cells, hyalinization of the interstitial tissue with no cells of Leydig; Case 6, mitotic figures present in the cells of the seminiferous tubules and normal cells of Leydig.

The findings in the ovaries were as follows: Case 4, ovaries small and fibrous; Case 7, ovarian tissue replaced by corpora albicantes and



fibrous tissue, germinal follicles absent; Case 8, dense stroma without evidence of germinal epithelium or follicle development, two small cysts lined with epithelium. Cushing and Davidoff<sup>24</sup> described the ovarian findings in a case previously reported by Cushing.<sup>20</sup> In this instance the ovary might have been "regarded as normal were it not for the history of 3 years of amenorrhoea." There were 4 large, fully developed Graafian follicles, the ova of which appeared normal and ready for ovulation. There were no corpora atretica and only one or two faint relics of old corpora albicantia. It appears that both testes and ovaries may be affected in various degrees in acromegaly, the microscopic picture of these organs varying from normal to advanced atrophy.

*Chromophobe Adenomas.*—Although chromophobe adenomas are much more common than the acidophilic type, very few post-mortem reports are available in the literature. Cushing and Davidoff<sup>24</sup> stated that they had "only two autopsies to draw upon for desired information." These were apparently Cases 5 and 15 in Cushing's<sup>20</sup> monograph on the pituitary body (1912). The findings in these cases will be mentioned later. In order to obtain a more comprehensive view of the endocrine post-mortem findings in cases of chromophobe adenoma, Table VIII was compiled from the autopsy protocols of 9 cases of Cushing's series in the Brain Tumor Registry, Yale University School of Medicine.\*

*Thyroid.*—The thyroid gland was small or atrophied in 4 of 8 cases, in 2 of which fibrosis was noted. It was likewise small in Cushing's Case 5, but there was excess of colloid in distended acini. The gland was normal in 3 instances, in 2 of which the colloid was mentioned as being abundant. Enlargement of the thyroid was observed in 1 case, the acini being distended with colloid. The trend is obviously toward inactivity of the thyroid gland although an abundance of colloid is not unusual.

*Parathyroids.*—Specific reference to the parathyroids was found in only two protocols. They were normal in 1 case and fat cell replacement was noted in the other. Further information concerning the parathyroids is certainly desirable.

*Thymus.*—The thymus was unusually large in 1 case, its weight being 40 Gm. It measured 5 x 3 cm. in a second case. From the absence of specific mention of the thymus in the other protocols, it may be assumed to have been small or absent. In Cushing's Case 5 it weighed 30 Gm. and showed extreme hyperplasia; in his Case 15 it was represented by mere shreds of involuted thymic tissue, containing an occasional Hassall corpuscle. It must be admitted that thymic persistence or even enlargement may be observed occasionally in conjunction with chromophobe adenoma of the pituitary.

*Adrenals.*—The adrenals were small or atrophic in 5 of 8 cases and normal in 3. In one instance the atrophy was noted to be chiefly in the

\*With the kind assistance of Dr. Louise Elsenhardt.

TABLE VIII  
POST-MORTEM FINDINGS IN CHROMOPHOBE ADENOMA

CASE	SEX	AGE	THYROID	PARA-THY-ROIDS	THY-MUS	AD-RENALS	PAN-CREAS	GONADS	CAUSE OF DEATH
C. W.	M	62	Atrophy, fibrosis			Normal	Normal	Atrophy, fibrosis	Extradural hemorrhage
C. K.	F	58	Small			Small	Normal	Atrophy	Cardiac failure
W. C.	M	22	Large, colloid		5 x 3 cm.	Small 5 and 6 Gm.	Normal	Atrophy, 14 Gm. each	Postoperative
P. H.	M	35					Fibrosis		Sphenoiditis (no operation)
F. K.	M	37	Atrophy, 23 Gm.	Fat replacement	Large, 40 Gm.	Cortical atrophy, 3.4 and 3.2 Gm.	Normal	Atrophy, 11.5 and 12.5 Gm.	Postoperative, intracranial extension
T. H.	M	49	Normal			Cortical fibrosis	Normal		Cerebral hemorrhage (operation 5 years earlier)
J. A.	M	54	Small			Atrophy	Normal	One normal	Extension of growth
B. K.	M	56	Normal	Normal		Normal	Normal	Atrophy	Postoperative (elsewhere)
M. J.	F	40	Normal			Normal	Some large islets	Atrophy	Septicemia (operation earlier admission)

fascicular zone of the cortex; another showed slight cortical fibrosis, while a third was described as having atrophy of both the cortex and medulla. One pair of "small" glands (5 and 6 Gm.) revealed normal structure microscopically but the cells contained "considerable lipoid." The adrenals in Cushing's Case 5 were described as "very large," with "extreme fatty degeneration of the reticular cells"; the medulla was "exceedingly small" but the cells appeared normal. In his Case 15 the adrenals were "practically normal." The slight but definite tendency toward adrenal atrophy in the presence of chromophobe adenoma of the pituitary is in striking contrast to the reverse tendency in acidophilic and basophilic adenomas.

*Pancreas.*—The pancreas was reported to be normal in 7 of 9 cases. In one of the remaining cases, slight diffuse fibrosis including the islands of Langerhans was described; in the other, some of the islands were "enormous." In contrast to this last case, Cushing's Case 5 was described as "islets inconspicuous, small, apparently normal." It appears that the pancreas may be expected to be normal in the presence of a chromophobe adenoma of the pituitary.

*Gonads.*—Atrophy of the gonads was noted in 6 of 7 cases. In the remaining case, one testicle was undescended, small, firm and atrophic;

the other was normal. The histologic picture of the testes was as follows: C. W., moderate atrophy and fibrosis with almost complete absence of spermatogenesis; W. C., "not much spermatogenesis"; F. K., atrophy with loss of germinative epithelium, interstitial cells not identified; B. K., inactive spermatogenesis. In Cushing's Case 5 there was absence of interstitial cells, normal tubules, Sertoli cells present, and some spermatozoa. In his Case 15 there were "normal tubules and spermatozoa but no interstitial cells which can be identified as such."

The ovaries were atrophied in both women in the series. C. K. had a menopause at the age of 52 and was operated upon for a chromophobe adenoma of the pituitary at the age of 53 years. She died of cardiac failure in her fifty-eighth year and the ovaries were "small and atrophic." M. J. had onset of amenorrhea at the age of 30 years and a transphenoidal removal of a pituitary adenoma was done at the age of 40 years. She died from septicemia, the result of urinary infection, six weeks later. The right ovary was replaced by a large cyst; the left ovary was grossly atrophic but its histologic characteristics were not included in the protocol. Unfortunately neither case is suitable for an analysis of the ovarian changes associated with chromophobe adenoma of the pituitary. In the male, gonadal atrophy is a striking feature; it is probable that this is likewise true in the female.

*Basophilic Adenomas.*—In spite of the fact that the basophilic adenoma has been recognized as a clinical entity only since 1932 (Cushing<sup>22</sup>), a considerable body of information has been accumulated concerning the post-mortem findings. This is due chiefly to Eisenhardt and Thompson,<sup>28</sup> and to the stimulating influence of Cushing. Table IX is compiled from the tabulation of Eisenhardt and Thompson,<sup>28</sup> based upon the post-mortem findings in 67 cases of pituitary basophilism, 47 of the patients having basophilic adenomas of the pituitary. Those patients having merely microscopic conglomerations of basophilic elements, sometimes described as adenomas, were excluded from consideration by Eisenhardt and Thompson.

*Pituitary.*—Basophilic adenomas rarely attain sufficient size to expand the sella turcica or extend above the diaphragm sellae. Compression of the remaining portion of the pituitary gland is not a striking feature. The most frequent effects noted in the gland itself are the Croke<sup>17</sup> changes. This hyalinization of the cytoplasm of the basophilic cells of the anterior lobe was definite or questionable in 95 per cent of the 44 cases in which the protocols included it. Its significance was interpreted by Croke<sup>17</sup> as an expression of altered physiologic activity of the basophilic cells. Severinghaus and Thompson<sup>16</sup> were of the opinion that the Croke changes represent degenerative manifestations following a period of physiologic overactivity of the basophiles as a reciprocal consequence of inactivation of certain subsidiary ductless glands.

TABLE IX  
POST-MORTEM FINDINGS IN BASOPHILIC ADENOMA  
(EISENHARDT AND THOMPSON, 47 CASES)

	PER CENT
Pituitary: Crooke changes	
Definite	70
Questionable	25
Adrenal hyperplasia (adenoma 17%)	83
Gonads atrophic	85
Parathyroids:	
Normal	54
Atrophy	23
Hyperplasia or adenoma	23
Thymus atrophic or absent	90
Thyroid:	
Inactive or small	47
Colloid goiter or large	32
Normal	15
Adenomas	6

*Adrenals.*—Hyperplasia of the adrenals was noted in 83 per cent of the 35 cases in which this feature was included in the protocols. An example of the extreme degree of adrenal enlargement which may occur is the case of Page, Roberts, and Biggart,<sup>61</sup> with adrenal weights of 26 Gm. for the right gland and 34 Gm. for the left. Furthermore, adrenal adenomas were present in 17 per cent of the 35 cases. Although the type of adenoma was not specified in most of the cases, they were presumably cortical in origin. There can be no doubt that adrenal hyperplasia is a prominent feature of the endocrine complex associated with basophilic adenoma of the pituitary.

*Gonads.*—Gonadal atrophy was reported in 85 per cent of 33 cases in which the protocols contained a definite statement concerning this feature. There was a slight sex difference, atrophy being noted in 8 of 11 males compared with 19 of 22 females. Atrophy of the gonads is unquestionably an outstanding element in the pathologic picture of the basophilic adenomas.

*Parathyroids.*—Specific reference to the parathyroids appeared in 22 instances, the glands being described as normal in 54 per cent. Atrophy was noted in 23 per cent while hyperplasia or adenoma formation occurred in 23 per cent. The presence of parathyroid adenomas in 4 of the 22 cases is likely significant in view of the skeletal decalcification which appeared in 85 per cent of the entire series of 47 cases (Table V).

*Thymus.*—The state of the thymus was noted in 20 cases and was reported as atrophic or absent in 90 per cent of this number. It was "large" in 1 patient, a male of 19 years of age, and "persistent" in another, a female aged 20 years.

*Thyroid.*—The thyroid was described in 34 cases and was reported to be inactive (13 cases) or small (3 cases) in 47 per cent. The thyroid was large (4 cases) or a colloid goiter (8 cases) was present in 32 per

cent. The gland was probably normal (5 cases) in 15 per cent, although "abundant colloid" was mentioned in 1 of these. Adenomas (2 cases) were found in 6 per cent. The variability of the post-mortem appearance of the thyroid gland is not surprising in view of the diverse findings concerning basal metabolic rate: Above +15, 25 per cent; below -15, 25 per cent (Table V).

#### CLINICAL, PATHOLOGIC AND EXPERIMENTAL CORRELATION

Critical surveys of the field of pituitary endocrinology have been published by Van Dyke<sup>92</sup> in 1936 and 1939. The Association for Research in Nervous and Mental Disease<sup>75</sup> published a monograph on the pituitary gland in 1938. More recent developments in this field have been covered in the yearly volumes of the Annual Review of Physiology by Evans,<sup>31</sup> Thomson and Collip,<sup>91</sup> Soskin,<sup>87</sup> Riddle,<sup>67</sup> Long,<sup>55</sup> Hisaw and Astwood,<sup>42</sup> Houssay and Deulofeu,<sup>43</sup> Pfeiffer,<sup>62</sup> and in brief reviews by Collip<sup>14</sup> and Young.<sup>94</sup> The literature for 1940 to 1942 has been reviewed by Hildebrand and Rynearson.<sup>41</sup> In spite of an amazing amount of experimental studies upon the endocrine functions of the hypophysis,\* sufficient data are not yet available for complete explanation of all clinical and pathologic findings previously discussed. Apparently contradictory results in some instances are due to species differences in experimental animals. Another source of conflict is the diverse methods of preparing pituitary extracts. On the basis of the physiologic actions of such extracts, at least sixteen effects might be ascribed to the anterior hypophysis as follows: (1) stimulation of general body growth; (2) thyrotropic effect; (3) probably two gonadotropic actions; (4) adrenocortical effect; (5) adrenomedullary effect; (6) mammary secretory action; (7) diabetogenic, (8) ketogenic, (9) glycotropic and glyco-static actions; (10) liver fat and (11) blood lipid effects; (12) inhibition of insulin hypoglycemia; (13) inhibition of adrenalin hyperglycemia; (14) lowering of respiratory quotient; (15) specific metabolic principle; (16) chromatophore- and erythrophore-expanding effects. In spite of this imposing list of physiologic effects, it is likely that not more than three, and probably only two cell types, acidophilic and basophilic are responsible for the elaboration of anterior pituitary hormones.

Several factors merit consideration in evaluation of the results of experimental studies on the effects of anterior pituitary extracts. None of the anterior pituitary hormones have been synthesized and few have been isolated in a form approaching chemical purity. Many of the extracts, although having physiologic effects, have not yet been proved to be true hormones. The response of the endocrine system in general, to these biologic products, undoubtedly influences the resultant physiologic picture. In fact, the subsidiary endocrine responses may in turn

\*The neurohypophysis is omitted from this discussion since tumors do not arise in the posterior pituitary.

alter the function of the hypophysis. It is not surprising, therefore, that numerous physiologic functions have been attributed to the anterior pituitary. However, the opinion of such authorities as Collip<sup>44</sup> and Severinghaus<sup>45</sup> suggests that the number of true anterior lobe hormones must be very small. The various physiologic effects may be represented by different groupings in two or three protein substances, the true anterior lobe hormones.

The pituitary is now well recognized as the master gland of the endocrine system, a role forecast by Cushing many years ago. The accumulation of a large body of clinical, pathologic, anatomic, physiologic and biochemical studies upon this gland allows, at this time, a considerable degree of correlation in terms of specific cellular function within the hypophysis. There is sound anatomic evidence (Severinghaus<sup>45</sup>) for the belief that a secretory cycle normally occurs in the cells of the anterior pituitary, the chromophobes becoming acidophiles or basophiles by a process of granulation; later returning to the chromophobe state through degranulation. The proportions and appearances of the actively secreting acidophiles and basophiles are strikingly influenced by such changes as pregnancy, castration, hyperthyroidism, or thyroidectomy. Cytologic studies indicate that the chromophobes cannot be regarded as actively secreting cells. At present, indirect experimental evidence must be relied upon to corroborate the clinical and pathologic findings in regard to the specific physiologic secretions of the acidophiles and basophiles respectively. The effects of injections of extracts prepared from human acidophilic and basophilic adenomas might be expected to yield valuable information in this respect; a start in this direction has already been made by Kraus.<sup>50</sup> The anterior pituitary of the dwarf mouse, completely lacking acidophiles (Smith and MacDowell<sup>85</sup>), likewise might be suggested for similar experimental use.

*Growth.*—Clinical and pathologic evidence—gigantism, acromegaly, organomegaly—presents strong support for the belief that a growth hormone is produced by the acidophiles. The experimental evidence begins with the studies of Smith,<sup>79</sup> in 1918, demonstrating that the growth rate of tadpoles was accelerated by anterior pituitary feeding. In 1921, Evans and Long<sup>82</sup> showed that mammalian gigantism could be produced in the rat by long-continued injection of a simple extract of the anterior pituitary. Two years later Smith and Smith<sup>86</sup> found that growth-promoting effects could be produced by ox pituitary tissue composed of acidophiles and chromophobes but not by tissue composed of basophiles and chromophobes. The absence of acidophiles in the pituitary of dwarf mice (Smith and MacDowell<sup>84</sup>) has already been mentioned.

More recent developments indicate that the growth factor may be separated from other fractions of pituitary extracts. The chief function of the growth hormone appears to be the general control of orderly

body growth. Epiphyseal closure follows hypophysectomy and this may be prevented in experimental animals by injections of the growth factor. The growth effect of anterior pituitary extracts is absent in thyroidectomized rats and is increased by the combination of growth and thyrotropic factors. Human gigantism may be arrested and epiphyseal closure effected by administration of testosterone. Growth is depressed by estrone or estradiol therapy; however, immense doses of estrogen are followed by acidophilic hyperplasia of the human anterior pituitary. Growth ceases in intense diabetes in spite of injections of anterior pituitary extract containing the growth factor.

*Gonads.*—Clinical and pathologic studies leave little doubt that gonadal function is altered—amenorrhea, impotentia, loss of libido—in the presence of either acidophilic or basophilic adenomas of the pituitary. However, the exact nature of this alteration is not clear at present. The microscopic picture of the gonads in acromegaly varies from normal to advanced atrophy; the atrophy, in the testes, apparently involves both tubules and interstitial cells. The cytologic changes in the gonads in pituitary basophilism is likewise uncertain. Of 16 cases reviewed by Cushing<sup>21</sup> the ovaries were “senile” in Case 3; there was “follicular atresia” in Case 4; they were “small but histologically normal” in Case 6; in Case 7 “the ovaries were enlarged apparently from increase in stroma; there was a single large corpus luteum with a small central hemorrhagic area and several smaller ones in various stages of organization.” The testes in Case 9 showed “fibrosis with atrophic changes, though some active spermatogenesis was still present”; in Case 10 spermatides, spermatoblasts, and spermatozoa were absent and the interstitial cells were diminished.

Cytologic studies of the pituitary following castration in the rat reveal a marked increase in the number of basophiles, with vacuolated cytoplasm, and a decrease in size and number of acidophiles. Similar changes in the basophiles of the castrate human hypophysis were found by Biggart,<sup>11</sup> but varying response of the acidophiles was noted. The cellular changes in the hypophysis of the guinea pig during pregnancy have been shown by Kirkman<sup>48</sup> to consist of an increase of degranulated basophiles rich in mitochondria—evidence of active secretion; prior to parturition a significant increase of acidophiles occurs. Similar changes have been noted in the human hypophysis by Severinghaus.<sup>75</sup> The correlation of these changes with the physiologic evidence of large quantities of gonadotropic hormone appearing during pregnancy is complicated by the fact that a luteinizing factor (prolan) is produced by the chorionic epithelium of the placenta. However, it appears that the anterior pituitary produces a luteinizing factor, at least during the early phase of pregnancy; there is reason to believe that this factor is elaborated by the basophiles. The hypophysis of the human fetus, lacking basophiles, appears to contain small amounts of follicle-stimulating hormone but no luteinizing hormone (Philipp<sup>63</sup>).

Recent experimental developments, based upon the pioneer work of Smith and Engle<sup>79</sup> and Zondek and Aschheim,<sup>80</sup> indicate that two separable fractions of gonadotropic hormone are probably produced by the anterior pituitary: (1) follicle-stimulating hormone (F.S.H.), necessary for follicle maturation; (2) luteinizing hormone (L.H.). A third factor (leutotropin) has been suggested, necessary for the secretion of progesterone by the corpus luteum, and possibly related to the lactogenic factor of the anterior pituitary. Tubular growth in the testes is dependent upon the follicle-stimulating factor; the luteinizing factor or interstitial cell-stimulating hormone (I.C.S.H.) is responsible for maintenance of the interstitial cells of the testes and production of male hormone. The production of estrogen by growing ovarian follicles is dependent upon the combination of F.S.H. with a small amount of L.H. Ovulation and corpus luteum formation require a level of L.H. much higher than that necessary to maintain the interstitial cells of the ovary or testis. Numerous studies have been made upon the effects of estrogen therapy upon the pituitary. There are cytologic evidences for increased secretory activity by both acidophiles and basophiles, especially the latter; excessive doses of estrogen may result in extreme enlargement of the pituitary and "adenoma" formation. The decrease in F.S.H. and L.H. potency of the pituitary (animals and human) following estrogen therapy may be explained by release of gonadotropic hormone from the pituitary (Severinghaus<sup>81</sup>). Testosterone apparently decreases the gonadotropic potency, especially L.H. of the rat pituitary.

*Thyroid.*—The frequent occurrence of thyroid enlargement, usually of the colloid type, and increased basal metabolic rate in acromegaly suggest that a thyrotropic factor may be secreted by the acidophiles. The effects of pituitary basophilism upon the thyroid are less constant, although the thyroid is enlarged in about one-third of the cases and the basal metabolism elevated in about one-fourth.

Cytologic studies of the anterior pituitary after thyroidectomy indicate that both types of chromophiles are affected; there are loss of acidophiles and castration-like changes in the basophiles. Experimental hyperthyroidism results in evidences of increased secretory activity of the acidophiles, but the basophiles demonstrate castration-like changes with increase in size and number and vacuolization.

Experimental evidence for the dependence of thyroid activity upon the anterior pituitary, previously suspected, was placed upon a sound basis by Smith.<sup>81</sup> The thyroid atrophies after hypophysectomy and the basal metabolic rate is decreased. Hyperplasia of the thyroid and increased basal metabolic rate follow injections of appropriate anterior pituitary extracts. The thyrotropic factor appears to be a separable fraction of the anterior pituitary, affecting the thyroid by: (1) influence on the rate of discharge of secretion and (2) changes in the



morphologic structure of the gland. However, the thyroid response to iodine is retained after hypophysectomy. Thyroidectomy appears to suppress F.S.H. in the male mouse pituitary.

*Adrenals.*—Hyperplasia of the adrenals is a prominent feature of the post-mortem findings in both acromegaly and pituitary basophilism. However, it is difficult to ascribe specific features of the respective clinical syndromes to the adrenal pathology. The similarity of the clinical pictures of pituitary basophilism and of certain adrenal cortical tumors would appear to be more than a mere coincidence. However, the most striking adrenal hyperplasia is found in conjunction with acidophilic rather than basophilic adenomas. There is a definite tendency toward the formation of adrenal cortical adenomas in both instances. Cytologic changes in the human anterior pituitary in adrenal insufficiency appear to involve a considerable reduction in the number of both acidophiles and basophiles, with the appearance of abnormal transitional basophiles.

The experimental work of Smith<sup>82</sup> demonstrated that adrenal cortical atrophy, following hypophysectomy, could be prevented by intramuscular implantation of fresh rat pituitaries. The pituitary is necessary for the compensatory hypertrophy of the remaining adrenal after unilateral adrenalectomy. The adrenocortical factor appears to be a separable fraction, distinct from the thyrotropic factor. The existence of a medullotropic factor has been suggested by Collip.<sup>15</sup> Recent developments suggest that pituitary basophilism may be differentiated from certain cases of masculinizing adrenal cortical tumors by the great increase in 17-ketosteroids in the latter. Castration is followed by a reduction in 17-ketosteroids.

*Pancreas.*—The high incidence of decreased sugar tolerance, glycosuria, and diabetes mellitus in both acromegaly and pituitary basophilism suggests the possibility of a direct effect of the anterior pituitary upon the islet tissue of the pancreas. Post-mortem findings in the pancreas of acromegalics have been equivocal; there are insufficient data to evaluate the state of the pancreas in pituitary basophilism. The results of cytologic studies of the anterior pituitary, following pancreatectomy or repeated injections of insulin, have been rather contradictory with respect to the nature of the cell changes, but consistent in implicating the acidophiles.

Experimental evidence begins with the demonstration by Houssay and Deulofeu,<sup>43</sup> that hypophysectomy increases the sensitivity to insulin and diminishes the severity of diabetes following pancreatectomy; that the reverse effects may be produced by administration of suitable anterior pituitary extracts, eventually leading to a diabetic state. Later, it was shown by Young<sup>94</sup> that a permanent diabetic state can be produced by repeated injections of appropriate anterior pituitary prepara-

tions, with consequent depletion of the cytoplasmic granules of the beta cells and hyaline replacement of the islets of Langerhans. The insulin content of such organs is much reduced but normal islet tissue may be restored by insulin treatment. There appears to be an early phase in the islet response to anterior pituitary extract during which the islet tissue and insulin content of the pancreas are increased. There is reason to suspect that the diabetogenic and panereotropic principles are closely related to the growth-promoting factor of the anterior pituitary.

*Thymus.*—The frequent enlargement of the thymus in acromegaly is difficult to evaluate in view of the occasional thymic enlargement in chromophobe adenomas. Thymic atrophy appears to be the rule in basophilic adenomas.\* Cytologic studies indicate that administration of thymus extract is followed by a definite increase in the percentage of pituitary acidophiles in young rats, especially males. Experimental evidence is somewhat conflicting but there is a suggestion that the thymus promotes growth and development. Administration of anterior pituitary extracts hastens thymic involution except in dwarf mice, where the anterior pituitary growth factor causes thymic proliferation. However, hypophysectomy accelerates involution of the thymus in young dogs or rats, but thymic hypertrophy may occur in adult rats. Atrophy of the thymus is produced by injections of testosterone propionate or estrone, in rats, while hypertrophy follows castration.

*Parathyroids.*—The high incidence of skeletal decalcification in pituitary basophilism suggests the possibility of parathyroid involvement; in fact, parathyroid hyperplasia or adenoma formation were present in a significant number of cases. However, the few studies which have been reported on calcium and phosphorous balance<sup>2</sup> in pituitary basophilism have failed to reveal abnormalities as striking as those of hyperparathyroidism. Parathyroid hyperplasia or adenoma formation has been noted occasionally in acromegaly.

A study of the pituitary changes in male rats after parathyroidectomy or repeated injections of parathyroid hormone suggests that the former is followed by an increase in acidophiles, the latter by a decrease in these cells. Cytologic studies of the parathyroids in experimental animals suggest that parathyroid atrophy may follow hypophysectomy while hypertrophy of the glandules with hyperplasia of the chief cells has been reported after injections of anterior pituitary extracts. However, similar effects are produced by injections of pregnancy urine or estrone. Effects upon calcium levels are equivocal. Calcemia and hypercalcification of bones may be produced in some animals by estrogen; the bone changes are inhibited by testosterone.<sup>35</sup> It may be significant that estrogen has been reported to be decreased or absent in Cushing's disease, and the urinary androgens increased.<sup>3</sup>

*Mammary Glands.*—Occasional instances of persistent lactation have been reported in acromegaly; mammary hypoplasia is not infrequent

\*Cushing's syndrome was present in 3 cases of thymic tumor (Table VI).

in patients with chromophobe adenomas. Experimental evidence indicates that a lactogenic factor, prolactin, may be obtained as a separable fraction from the anterior pituitary and is probably elaborated by the acidophiles. Both the hypophysis and thyroid hormone are necessary for lactation in mice. Estrogen apparently increases the amount of prolactin in the anterior pituitary of rats, but estrogens have been used to suppress or inhibit lactation in human acromegaly. The promotion of mammary duct growth appears to be a function of estrogen, although this effect is absent in hypophysectomized animals. The presence of a mammogenic hormone in the anterior pituitary has been suggested. Growth hormone may produce limited mammary development in hypophysectomized rats.

*Metabolic Effects.*—Clinical evidence of general metabolic effects is present in all types of pituitary adenomas. The excessive tissue growth of gigantism and acromegaly, the frequent gain in weight with a chromophobe adenoma, and the peculiar selective obesity of pituitary basophilism, all appear to be external manifestations of altered metabolic processes.

Effects upon carbohydrate metabolism have been recognized for some time; the decreased sugar tolerance and tendency toward diabetes in acromegaly, the increased sugar tolerance in chromophobe adenomas—both are familiar examples. Now it appears that basophilic adenomas are frequently associated with decreased sugar tolerance and occasional mild diabetes. The relation of these diabetic tendencies to the pancreas has already been discussed. However, there is evidence that the effect on carbohydrate metabolism is not limited to the islets of the pancreas but occurs in all tissues; the much-discussed insulin resistance of "pituitary diabetes" may be a clinical example of this. Experimental evidence concerning the relationship of the anterior pituitary to carbohydrate metabolism has been reviewed recently by Russell.<sup>70</sup> Hypophysectomized animals exhibit a rapid decline in blood sugar, depletion of liver and muscle glycogen, and elevation of respiratory quotient, when fasted. These effects may be prevented by administration of anterior pituitary extract (glycostatic effect), and are apparently due to acceleration of peripheral oxidation of carbohydrate. Hypersensitivity to insulin follows hypophysectomy while insulin resistance (glycotropic effect) may be produced by administration of suitable anterior pituitary extract. A ketogenic factor is also recognized in anterior pituitary extracts. Intermediate effects of the anterior pituitary through the thyroid appear to be limited to alteration of general metabolic rate and the rate of intestinal absorption of carbohydrate. The situation with respect to the adrenals is more complex but there is evidence for a synergistic effect between the anterior pituitary and adrenocortical hormones. In addition, it appears that while the anterior pituitary effect is chiefly repression of *peripheral* carbohydrate oxida-

tion and promotion of muscle glycogen deposition, the adrenocortical hormone exerts a similar effect in the liver. The gluconeogenetic action of anterior pituitary extracts appears to be mediated through the adrenal cortex. Hypergluconeogenesis has been suggested as a probable explanation for the alterations in carbohydrate and protein metabolism observed in Cushing's syndrome.<sup>2</sup>

Anterior pituitary effects on protein metabolism have been suspected in acromegaly and gigantism. The observation of decreased nitrogen excretion following administration of the growth factor adds experimental confirmation. Conversely, hypophysectomy is followed by increased nitrogen loss. Two mechanisms have been suggested by which the anterior pituitary may affect protein metabolism: (1) by direct action on muscles, stimulating protein catabolism; (2) by indirect action through the pancreas, stimulating protein anabolism. The first effect may be mediated through the thyroid, since thyroid administration has been shown to increase protein catabolism and nitrogen excretion. Alterations in protein metabolism may also be mediated through the adrenal cortex, since cortical hormone appears to influence the deamination of amino acids, the formation of carbohydrates from keto acids derived from amino acids, and the gluconeogenesis from endogenous protein; the net result is stimulation of protein catabolism. The observation of a negative nitrogen balance in certain patients with pituitary basophilism has been suggested to be explainable on the basis of an adrenocortical effect. Studies upon the specific dynamic action of protein indicate that this action is diminished by hypophysectomy.

Effects upon fat metabolism might be expected on the basis of the frequent clinical finding of obesity in cases of chromophobe adenoma and pituitary basophilism. However, in the former at least, the weight gain may be explained by the lowered basal metabolic rate. Experimental evidence is provided by the observations of increased peripheral fat and decreased liver fat after hypophysectomy.<sup>71</sup> Conversely, liver fat is increased and fat mobilization accelerated by anterior pituitary administration.

A specific metabolic principle in the pituitary has been suggested by Collip.<sup>14</sup> The elevation of basal metabolic rate of thyroidectomized an-

TABLE X  
PROBABLE ENDOCRINE EFFECTS OF SPECIFIC PITUITARY CELL TYPES

EFFECT	ACIDOPHILES	BASOPHILES
Growth	+	
Gonads	+	+
Thyroid	+	?
Adrenals	+	+
Pancreas	+	
Thymus	?	
Parathyroids		?
Mammary glands	+	
Metabolic effects	+	+

imals by administration of crude pituitary extract, anterior lobe extract, or prolactin suggests the existence of such a metabolic principle. Administration of a potent preparation containing this principle is followed by a sharp elevation in basal metabolic rate and depression of the respiratory quotient. It has been suggested that this principle specifically stimulates the metabolism of fat. The metabolic principle is thought to have its origin in the pars intermedia of the pituitary.

*Résumé.*—Although further evidence is desirable concerning many of the effects ascribed to specific cells of the anterior pituitary, it is possible to give a tentative outline, based upon available information (Table X). Many of the symptoms of pituitary basophilism (skeletal decalcification, vascular hypertension, erythrocytosis, exophthalmos) await adequate explanation.

#### REFERENCES

1. Addison, W. H. F.: The Cell-Changes in the Hypophysis of the Albino Rat After Castration, *J. Comp. Neurol.* 28: 441, 1917.
2. Albright, F., Parson, W., and Bloomberg, E.: Cushing's Syndrome Interpreted as Hyperadrenocorticism Leading to Hyperglucocoenogenesis. Results of Treatment With Testosterone Propionate, *J. Clin. Endocrinol.* 1: 375, 1941.
3. Albright, F., Smith, P. H., and Richardson, A. M.: Postmenopausal Osteoporosis, *J. A. M. A.* 116: 2465, 1941.
4. Anderson, E. M., and Collip, J. B.: Thyreotropic Hormone of Anterior Pituitary, *Proc. Soc. Exper. Biol. & Med.* 30: 680, 1933.
5. Atkinson, F. R. B.: *Acromegaly*, London, 1932, John Bale Sons & Danielsson, Ltd.
6. Bakinski, J.: Tumeur du Corps Pituitaire sans Acromégalie et avec Arête de Développement des Organes Genitiaux, *Rev. neurol.* 8: 531, 1900.
7. Bailey, P.: Cytological Observations on the Pars Buccalis of the Hypophysis Cerebri of Man, Normal and Pathological, *J. M. Research* 42: 349, 1921.
8. Bailey, P., and Cushing, H.: Studies in Acromegaly. VII. The Microscopical Structure of the Adenomas in Acromegalic Dispituitarism (Fugitive Acromegaly), *Am. J. Path.* 4: 545, 1928.
9. Bartlett, F. K.: A Case of Acromegaly and Polyglandular Syndrome, With Special Reference to the Pineal Gland, *Arch. Int. Med.* 12: 201, 1913.
10. Benda, C.: Beiträge zur normalen und pathologischen Histologie der menschlichen Hypophysis cerebri, *Klin. Wchnschr.* 37: 1205, 1900.
11. Biggart, J. H.: The Hypophysis of the Human Castrate, *Bull. Johns Hopkins Hosp.* 54: 157, 1934.
12. Calder, R. M., and Porro, F. W.: Adenoma of Adrenal Cortex Simulating Pituitary Basophilism (Cushing Syndrome), *Bull. Johns Hopkins Hosp.* 57: 99, 1935.
13. Coggeshall, C., and Root, H. F.: Acromegaly and Diabetes Mellitus, *Endocrinology* 26: 1, 1940.
14. Collip, J. B.: The Physiology of the Anterior Pituitary and a Note on the Medullotrophic Hormone, *Am. J. Obst. & Gynec.* 39: 187, 1940.
15. Collip, J. B.: Demonstration of an Orally Active Medullotrophic Principle in a Primary Extract of Pituitary Tissue, *Canad. M. A. J.* 42: 2, 1940.
16. Courville, C., and Mason, V. R.: The Heart in Acromegaly, *Arch. Int. Med.* 61: 704, 1938.
17. Crooke, A. C.: A Change in the Basophil Cells of the Pituitary Gland Common to Conditions Which Exhibit the Syndrome Attributed to Basophil Adenoma, *J. Path. & Bact.* 41: 399, 1935.
18. Cunningham, D. J.: The Skeleton of the Irish Giant, Cornelius Magrath, *Tr. Roy. Irish Acad.* 29: 553, 1891.
19. Cushing, H.: Dyspituitarism, the Harvey Lecture of Dec. 10, 1910.
20. Cushing, H.: *The Pituitary Body and Its Disorders*, Philadelphia, 1912, J. B. Lippincott Company.
21. Cushing, H.: *Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System*, Springfield, Illinois, 1932, Charles C Thomas, Publisher.

22. Cushing, H.: The Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations (Pituitary Basophilism). *Bull. Johns Hopkins Hosp.* 50: 137, 1932.
23. Cushing, H.: Dyspituitarism: Twenty Years Later, The Harvey Lectures, 1932 to 1933.
24. Cushing, H., and Davidoff, L. M.: The Pathological Findings in Four Autopsied Cases of Acromegaly With a Discussion of Their Significance, No. 22, New York, 1927, Monograph Rockefeller Institute for Medical Research.
25. Davidoff, L. M.: Studies in Acromegaly. III. The Anamnesis and Symptomatology in One Hundred cases, *Endocrinology* 10: 161, 1926.
26. Davis, A. C.: The Thyroid Gland in 166 Cases of Acromegaly, *J. Clin. Endocrinol.* 1: 415, 1911.
27. Dott, N. M., and Bailey, P.: A Consideration of the Hypophysial Adenomata, *Brit. J. Surg.* 13: 314, 1925.
28. Eisenhardt, L., and Thompson, K. W.: A Brief Consideration of the Present Status of So-called Pituitary Basophilism, *Yale J. Biol. & Med.* 11: 507, 1939.
29. Engle, E. T.: The Effect of Daily Transplants of the Anterior Lobe From Gonadectomized Rats on Immature Test Animals, *Am. J. Physiol.* 88: 101, 1929.
30. Erdheim, J.: Zur normalen und pathologischen Histologie der Glandula thyroidea, parathyroidea und Hypophysis, *Beitr. z. path. Anat. u. z. allg. Path.* 33: 158, 1903.
31. Evans, H. M.: Endocrine Glands: Gonads, Pituitary, and Adrenals, *Ann. Rev. Physiol.* 1: 577, 1939.
32. Evans, H. M., and Long, J. A.: The Effect of the Anterior Lobe Administered Intraperitoneally Upon Growth, Maturity, and Oestrus Cycles of the Rat, *Anat. Rec.* 21: 62, 1921.
33. Fritzsche, and Klebs, E.: Ein Beitrag zur Pathologie des Riesenwuchses, Leipzig, 1884, F. C. W. Vogel, p. 89.
34. Fröhlich, A.: Ein Fall von Tumor der Hypophysis cerebri ohne Akromegalie, *Wien. Klin. Rundschau* 15: 883 and 906, 1901. (Reprinted: A. Research Nerv. & Ment. Dis. Proc. 20: 16, 1939. Partial English translation: Bruch, H.: The Fröhlich Syndrome, *Am. J. Dis. Child.* 58: 1282, 1939.)
35. Gardner, W. U., and Pfeiffer, C. A.: Inhibition of Estrogenic Effects on Skeleton by Testosterone Injections, *Proc. Soc. Exper. Biol. & Med.* 38: 599, 1938.
36. Geddes, A. C.: Report Upon the Examination of the Body of an Acromegalic Subject, *Edinburgh M.J.* 2: (N.S.) 218, 1909.
37. Gilford, H.: On a Condition of Mixed Premature and Immature Development, *Tr. Med.-Chir.* 80: 17, 1897.
38. Gilford, H.: Progeria: A Form of Senilism, *Practitioner* 73: 188, 1904.
39. Gilford, H.: The Disorders of Post-Natal Growth and Development, London, 1911, Adlard, p. 646.
40. Goldberg, M. B., and Lissner, H.: Acromegaly: A Consideration of Its Course and Treatment. Report of Four Cases With Autopsies, *J. Clin. Endocrinol.* 2: 477, 1942.
41. Hildebrand, A. G., and Ryncarson, E. H.: Review of the Literature on the Pituitary Gland (1940 and 1941), *Arch. Int. Med.* 71: 262, 1943.
42. Hisaw, F. L., and Astwood, E. B.: The Physiology of Reproduction, *Ann. Rev. Physiol.* 4: 503, 1942.
43. Houssay, B. A., and Deulofeu, V.: Metabolic Functions of the Endocrine System, *Ann. Rev. Physiol.* 5: 373, 1943.
44. Josefson, A.: Om endokrina skelett-och utvecklingsrubbingar, Stockholm, 1915, Isaac Marcus, p. 381.
45. Keith, Arthur: An Inquiry Into the Nature of the Skeletal Changes in Acromegaly, *Lancet* 1: 993, 1911.
46. Keith, A.: Progeria and Ateleiosis, *Lancet* 1: 305, 1913.
47. Kepler, E. J., Kennedy, R. L. J., David, A. C., Walters, W., and Wilder, R. M.: Suprarenocortical Syndrome and Pituitary Basophilism: Presentation of Three New Cases, *Proc. Staff Meet., Mayo Clin.* 9: 169, 1934.
48. Kirkman, H.: A Cytological Study of the Anterior Hypophysis of the Guinea Pig and a Statistical Analysis of Its Cell Types, *Am. J. Anat.* 61: 233, 1937.
49. Kon, J.: Hypophysenstudien. I. Seltene Tumoren der Hypophysengegend (Teratom, Peritheliom, telangiektatisches Sarkom). II. Über das Verhalten der Hypophyse nach Kastration, *Beitr. z. path. Anat. u. z. allg. Path.* 44: 233, 1908.

50. Kraus, E. J.: Welche Zellen der menschlichen Hypophyse bilden ausserhalb der Schwangerschaft das Vorderlappengeschlechtshormon (VLGH)? *Klin. Wehnschr.* 11: 1020, 1932.
51. Launois, P.-E., and Roy, P.: Gigantism et acromégalie; autopsie d'un géant acromégalique et diabétique, *Nouv. Iconogr. Salpêtr.* 16: 163, 1903.
52. Levi, E.: Contribution à l'étude de l'infantilisme du type Lorain, *Nouv. Iconogr. Salpêtr.* 21: 297, 1908.
53. Leyton, O., Turnbull, H. M., and Bratton, A. B.: Primary Cancer of the Thymus With Pleuriglandular Disturbance, *J. Path. & Bact.* 34: 635, 1931.
54. The Life Extension Examiners: A Study of Impairments Found Among 10,000 Unselected Examinees. Article I: Blood Pressure, *Proc. Life Ext. Exam.* 1: 66, 1939.
55. Long, C. N. H.: Metabolic Functions of the Endocrine Glands, *Ann. Rev. Physiol.* 4: 465, 1942.
56. Lorain, P.: Du féminisme et de l'infantilisme chez les tuberculeux. Thèse pour le Doctorat en Médecine. No. 1, 5, 1871. Introduction to thesis of Faneau de la Cour. Paris.
57. Marie, P.: Sur deux cas d'acromégalie, *Rev. de méd.* 6: 297, 1886.
58. Marie, P.: Sur la reviviscence du thymus, *Bull. et mém. Soc. méd. d. hôp. de Paris* 10: (series 3) 136, 1893.
59. Orianoff: Sur un cas d'épithélioma, 1892, Thèse de Paris.
60. Osborne, O. T.: A Case of Acromegaly: Autopsy: Skeleton, *Tr. A. Am. Physicians* 12: 262, 1897.
61. Page, A. P. M., Roberts, L. V., and Biggart, J. H.: Cushing's Syndrome in a Mulatto; With a Histological Report, *Lancet* 2: 625, 1937.
62. Pfeiffer, C. A.: Endocrinology of Reproduction, *Ann. Rev. Physiol.* 5: 413, 1943.
63. Philipp, E.: Über den Zusammenhang von Histologie und innersekretorischer Wirkung des Hypophysenvorderlappens, *Zentralbl. f. Gynäk.* 54: 3076, 1930.
64. Rasmussen, A. T.: The Percentage of the Different Types of Cells in the Male Adult Human Hypophysis, *Am. J. Path.* 5: 263, 1929.
65. Rasmussen, A. T.: The Relation of the Basophilic Cells of the Human Hypophysis to Blood Pressure, *Endocrinology* 20: 673, 1936.
66. Reinhardt, A., and Creutzfeldt, H. G.: Beitrag zur Lehre von der Akromegalie, *Beitr. z. path. Anat. u. z. allg. Path.* 56: 465, 1913.
67. Riddle, O.: Endocrine Aspects of the Physiology of Reproduction, *Ann. Rev. Physiol.* 3: 573, 1941.
68. Robinson, S. C.: The Range of Normal Blood Pressure, *Proc. Life Ext. Exam.* 1: 104, 1939.
69. Rösle, R.: Das Verhalten der menschlichen Hypophyse nach Kastration, *Virchows Arch. f. path. Anat.* 216: 248, 1914.
70. Russell, J. A.: The Relationship of the Anterior Pituitary to the Thyroid and the Adrenal Cortex in the Control of Carbohydrate Metabolism, *Essays in Biology—In honor of Herbert M. Evans*, Berkeley, 1943, University of California Press, p. 509.
71. Samuels, L. T., Reincke, R. M., and Ball, H. A.: Balance Studies in Hypophysectomized and Normal Rats Fed on Equicaloric High Carbohydrate and High Fat Diets, *Endocrinology* 31: 35, 1942.
72. Schultze, F., and Fischer, B.: Zur Lehre von der Akromegalie und Osteoarthropathie hypertrophante, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* 24: 607, 1912.
73. Severinghaus, A. E.: A Cytological Technique for the Study of the Anterior Lobe of the Hypophysis, *Anat. Rec.* 53: 1, 1932.
74. Severinghaus, A. E.: The Effect of Castration in the Guinea Pig Upon the Sex-Maturing Potency of the Anterior Pituitary, *Am. J. Physiol.* 101: 309, 1932.
75. Severinghaus, A. E.: The Cytology of the Pituitary Gland. The Pituitary Gland, A. Research Nerv. & Ment. Dis., Proc., Baltimore, 1938, Williams & Wilkins Company, p. 69.
76. Severinghaus, A. E., and Thompson, K. W.: Cytological Changes Induced in the Hypophysis by the Prolonged Administration of Pituitary Extract, *Am. J. Path.* 15: 391, 1939.
77. Silver, S.: Simmonds's Disease (Cachexia Hypophyseopriva), *Arch. Int. Med.* 51: 175, 1933.
78. Simmonds, M.: Ueber Hypophysisschwund mit tödlichem Ausgang, *Deutsche med. Wehnschr.* 40: 322, 1914.
79. Smith, P. E.: The Growth of Normal and Hypophysectomized Tadpoles as Influenced by Endocrine Diets, *Univ. California Publ., Physiol.* 5: 11, 1918.

80. Smith, P. E.: The Topographical Separation in the Bovine Anterior Hypophysis of the Principle Reacting With the Endocrine System From That Controlling General Body Growth, With Suggestions as to the Cell Types Elaborating These Excretions, *Anat. Rec.* 25: 150, 1923.
81. Smith, P. E.: The Disabilities Caused by Hypophysectomy and Their Repair, *J. A. M. A.* 88: 158, 1927.
82. Smith, P. E.: Hypophysectomy and a Replacement Therapy in the Rat, *Am. J. Anat.* 45: 205, 1930.
83. Smith, P. E., and Engle, E. T.: Experimental Evidence Regarding the Role of the Anterior Pituitary in the Development and Regulation of the Genital System, *Am. J. Anat.* 40: 159, 1927.
84. Smith, P. E., and MacDowell, E. C.: An Hereditary Anterior-Pituitary Deficiency in the Mouse, *Anat. Rec.* 46: 249, 1930.
85. Smith, P. E., and MacDowell, E. C.: The Differential Effect of Hereditary Mouse Dwarfism on the Anterior-Pituitary Hormone, *Anat. Rec.* 50: 85, 1931.
86. Smith, P. E., and Smith, I. P.: The Response of the Hypophysectomized Tadpole to the Intraperitoneal Injection of the Various Lobes and Colloid of the Bovine Hypophysis, *Anat. Rec.* 25: 150, 1923.
87. Soskin, S.: Metabolic Functions of the Endocrine Glands, *Ann. Rev. Physiol.* 3: 543, 1941.
88. Susman, W.: Adenomata of the Pituitary With Special Reference to Pituitary Basophilism of Cushing, *Brit. J. Surg.* 22: 539, 1935.
89. Teel, H. M.: Basophilic Adenoma of the Hypophysis With Associated Pluri-glandular Syndrome, *Arch. Neurol. & Psychiat.* 26: 593, 1931.
90. Thompson, K. W., and Eisenhardt, L.: Further Consideration of the Cushing Syndrome, *J. Clin. Endocrinology* 3: 445, 1943.
91. Thomson, D. L., and Collip, J. B.: Endocrine Glands, *Ann. Rev. Physiol.* 2: 309, 1940.
92. Van Dyke, H. B.: The Physiology and Pharmacology of the Pituitary Body, Chicago, 1936, 1939, University of Chicago Press.
93. Weber, F. Parkes: Cutaneous Striae, Purpura, High Blood-Pressure, Amenorrhea and Obesity, of the Type Sometimes Connected With Cortical Tumours of the Adrenal Glands, Occurring in the Absence of Any Such Tumour—With Some Remarks on the Morphogenetic and Hormonic Effects of True Hypernephromata of the Adrenal Cortex, *Brit. J. Dermat.* 38: 1, 1926.
94. Young, F. G.: The Pituitary Gland and Carbohydrate Metabolism, *Endocrinology* 26: 345, 1940.
95. Zondek, B., and Aschheim, S.: Hypophysenvorderlappen und ovarium. Beziehungen der endokrinen Drüsen zur Ovarialfunktion, *Arch. f. Gynäk.* 130: 1, 1927.



50. Kraus, E. J.: Welche Zellen der menschlichen Hypophyse bilden ausserhalb der Schwangerschaft das Vorderlappengeschlechtshormon (VLGH)? *Klin. Wehnschr.* 11: 1020, 1932.
51. Launois, P.-E., and Roy, P.: Gigantism et acromégalie; autopsie d'un géant acromégalique et diabétique, *Nouv. Iconogr. Salpêtr.* 16: 163, 1903.
52. Levi, E.: Contribution à l'étude de l'infantilisme du type Lorain, *Nouv. Iconogr. Salpêtr.* 21: 297, 1908.
53. Leyton, O., Turnbull, H. M., and Bratton, A. B.: Primary Cancer of the Thymus With Pleuriglandular Disturbance, *J. Path. & Bact.* 34: 635, 1931.
54. The Life Extension Examiners: A Study of Impairments Found Among 10,000 Unselected Examinees. Article I: Blood Pressure, *Proc. Life Ext. Exam.* 1: 66, 1939.
55. Long, C. N. H.: Metabolic Functions of the Endocrine Glands, *Ann. Rev. Physiol.* 4: 465, 1942.
56. Lorain, P.: Du féminisme et de l'infantilisme chez les tuberculeux. Thèse pour le Doctorat en Médecine. No. 1, 5, 1871. Introduction to thesis of Faneau de la Cour. Paris.
57. Marie, P.: Sur deux cas d'acromégalie, *Rev. de méd.* 6: 297, 1886.
58. Marie, P.: Sur la reviviscence du thymus, *Bull. et mém. Soc. méd. d. hôp. de Paris* 10: (series 3) 136, 1893.
59. Orianoff: Sur un cas d'épithélioma, 1892, Thèse de Paris.
60. Osborne, O. T.: A Case of Acromegaly: Autopsy: Skeleton, *Tr. A. Am. Physicians* 12: 262, 1897.
61. Page, A. P. M., Roberts, L. V., and Biggart, J. H.: Cushing's Syndrome in a Mulatto; With a Histological Report, *Lancet* 2: 625, 1937.
62. Pfeiffer, C. A.: Endocrinology of Reproduction, *Ann. Rev. Physiol.* 5: 413, 1943.
63. Philipp, E.: Über den Zusammenhang von Histologie und innersekretorischer Wirkung des Hypophysenvorderlappens, *Zentralbl. f. Gynäk.* 54: 3076, 1930.
64. Rasmussen, A. T.: The Percentage of the Different Types of Cells in the Male Adult Human Hypophysis, *Am. J. Path.* 5: 263, 1929.
65. Rasmussen, A. T.: The Relation of the Basophilic Cells of the Human Hypophysis to Blood Pressure, *Endocrinology* 20: 673, 1936.
66. Reinhardt, A., and Creutzfeldt, H. G.: Beitrag zur Lehre von der Akromegalie, *Beitr. z. path. Anat. u. z. allg. Path.* 56: 465, 1913.
67. Riddle, O.: Endocrine Aspects of the Physiology of Reproduction, *Ann. Rev. Physiol.* 3: 573, 1941.
68. Robinson, S. C.: The Range of Normal Blood Pressure, *Proc. Life Ext. Exam.* 1: 104, 1939.
69. Rössle, R.: Das Verhalten der menschlichen Hypophyse nach Kastration, *Virchows Arch. f. path. Anat.* 216: 248, 1914.
70. Russell, J. A.: The Relationship of the Anterior Pituitary to the Thyroid and the Adrenal Cortex in the Control of Carbohydrate Metabolism, *Essays in Biology—In honor of Herbert M. Evans*, Berkeley, 1943, University of California Press, p. 509.
71. Samuels, L. T., Reincke, R. M., and Ball, H. A.: Balance Studies in Hypophysectomized and Normal Rats Fed on Equicaloric High Carbohydrate and High Fat Diets, *Endocrinology* 31: 35, 1942.
72. Schultze, F., and Fischer, B.: Zur Lehre von der Akromegalie und Osteoarthropathie hypertrophiante, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* 24: 607, 1912.
73. Severinghaus, A. E.: A Cytological Technique for the Study of the Anterior Lobe of the Hypophysis, *Anat. Rec.* 53: 1, 1932.
74. Severinghaus, A. E.: The Effect of Castration in the Guinea Pig Upon the Sex-Maturing Potency of the Anterior Pituitary, *Am. J. Physiol.* 101: 309, 1932.
75. Severinghaus, A. E.: The Cytology of the Pituitary Gland. The Pituitary Gland, A. Research Nerv. & Ment. Dis., Proc., Baltimore, 1938, Williams & Wilkins Company, p. 69.
76. Severinghaus, A. E., and Thompson, K. W.: Cytological Changes Induced in the Hypophysis by the Prolonged Administration of Pituitary Extract, *Am. J. Path.* 15: 391, 1939.
77. Silver, S.: Simmonds's Disease (Cachexia Hypophyseopriva), *Arch. Int. Med.* 51: 175, 1933.
78. Simmonds, M.: Ueber Hypophysisschwund mit tödlichem Ausgang, *Deutsche med. Wehnschr.* 40: 322, 1914.
79. Smith, P. E.: The Growth of Normal and Hypophysectomized Tadpoles as Influenced by Endocrine Diets, *Univ. California Publ., Physiol.* 5: 11, 1918.

its entire bulk, are made up of thyroid tissue. In a number of reported cases this tissue has become functionally hyperactive, producing clinical hyperthyroidism. This rare tumor type, however, need not be discussed in this communication. Those interested may be referred to the recent publication of Emge, wherein the subject is reviewed.

For an understanding of the special group of dysontogenetic functional tumors with which we are more directly concerned, some understanding of the early embryology of the gonads is indispensable. These organs are derived from a cell mass which develops in the anterior or ventral portion of the mesonephros. In the earliest stage of gonadal development it is not possible to distinguish whether the organ is to develop as a testis or an ovary. It is of interest to note that in this undifferentiated phase groups of cells may be segregated, and that from such cells tumors may arise in later life, regardless of whether the gonad develops into testis or ovary. In the ovary this tumor variety is now well recognized as the so-called dysgerminoma. The corresponding tumor in the testis is the well-known seminoma. Histologically these two tumor types are identical. As might be expected from their derivation, neither of these tumors possesses endocrine properties.

At a slightly later stage the cells in the sex gland anlage exhibit a differentiation into zigzag anastomosing tubules converging toward the hilum. In the case of the testis these cords are the progenitors of the seminiferous tubules, and by linking up with mesonephric tubular structures the entire testicular apparatus is soon laid down, the Wolffian duct itself becoming the vas deferens. From our own immediate viewpoint, however, it is important to remember that in the ovary as well as the testis the same sex cord differentiation takes place, though in the ovary it is abortive and incomplete, and is soon followed, with overlapping, by a second differentiating process. To put it very figuratively, the second or feminine differentiation takes place over the fossil remains of the first or more characteristically male process. It is believed that in the fully developed ovary of later life vestiges of these originally male-directed cells may persist in its medullary portion and that it is from such potentially masculine cells that tumors may arise which in their structure exhibit some degree or other of testicular architecture and which have the capacity of producing the male sex hormone.

To this group the designation of arrhenoblastoma was given by Meyer, to whom we are indebted for much of our knowledge of this whole special group of ovarian tumors. The explanation given of the histogenesis of arrhenoblastoma, as throwing light upon their masculinizing effect, will probably have to be modified as our knowledge of sex differentiation increases. The possible role of organizers and determiners of sex in the ovarian cortex and medulla is now being stressed by

biologists and cannot be overlooked. Moreover, the intimate embryologic relationship of the adrenal cortex and the ovarian medulla make it easy to understand that certain adrenal cortical tumors, like the ovarian arrhenoblastoma, have masculinizing tendencies, and some investigators have suggested that the embryologic inclusion of testicular elements in the adrenal area may explain the masculinizing property of certain tumors of the adrenal.

On the other hand, it is of interest to note that tumors made up of adrenal tissue may occur in the ovary and that such tumors produce a masculinization syndrome quite indistinguishable from that of arrhenoblastoma. The intensive studies of the past two or three years have shown that both male and female sex hormones are produced in the adrenal cortex, and interesting relationships between these and desoxycorticosterone have been demonstrated, but we are still in the dark as to the exact nature of the corticogonadal mechanism which is so clearly important in the differentiation of sex characters.

With the appearance of the typical feminine differentiating processes in the ovary, the primitive follicular apparatus is soon formed by the clusterlike grouping of granulosa cells around the oögonia. According to Meyer, rests of redundant granulosa may be left over and from them may later arise the well-known granulosa cell tumors. Since the cells from which they arise have been predestined as feminine, it is not surprising that such tumors are feminizing in their effects through their production of the estrogenic hormone. Here again, evidence is accumulating to indicate that Meyer's original concept must be modified. There is increasing opinion that both granulosa and theca cells arise from differentiation in situ of the ovarian mesenchyme and that the derivation of the feminizing group of tumors must be traced back to a mesenchymal, that is, a progranulosa and prothecal, stage. Such tumors may therefore assume epithelial (granulosa) characteristics or histologically they may appear to be stromal (thecal) in character. To the former group the designation of granulosa cell carcinoma is applied; to the latter, thecoma. Acceptance of such a view makes it difficult to separate these two varieties of tumor as sharply as has been done by some authors. Indeed, it is common to find an intermingling of granulosa and thecal elements in one and the same tumor.

In either the granulosa or thecal tumor luteinization changes may take place, probably through an excitation of the same sequential pituitary effect exhibited in the conversion of the normal granulosa of the reproductive epoch into lutein cells. The luteinization changes in the tumors may be partial, constituting the so-called folliculome lipidique described first by Lecène, or they may involve the whole structure of granulosa tumors, which, in such cases, are usually of small size. Thus is produced the so-called luteoma. Concerning the latter tumor type there is still much discussion and uncertainty, chiefly because of the

difficulty in certain cases of determining whether a given tumor is of lutein or adrenal character. A number of instances have been recorded in which luteoma is said to have brought about masculinization phenomena, but the probabilities are that most of these have really been of adrenal nature. However, in view of recent experimental investigations which indicate that progesterone may actually produce certain masculinization phenomena, such an assumption cannot be taken for granted. This aspect of the general subject is still quite confused. For a fuller discussion on this point the reader may be referred to the recent article of Rottino and McGrath, who propose for this group of tumors of uncertain histogenesis the designation of masculinovoblastoma.

*Pathology.*—The feminizing tumors are characterized by marked individual variation in histologic pattern. The granulosa group, however, is usually readily distinguishable by the granulosa morphology of the constituent epithelial cells together with certain growth characteristics which appear to distinguish granulosa cells in general. Among these is a tendency to an arrangement in small clusters suggesting the appearance of the primitive follicles of the ovary, except for the inclusion of the germ cells, and also the tendency to form tiny areas of cystic liquefaction resembling the Call-Exner bodies seen in the granulosa of many species, especially the rodents.

The granulosa tissue may be quite diffuse, but more frequently it is divided by trabeculae of connective tissue into long columns, producing a cylindromatous pattern. Much less frequent is an arrangement in spherical masses, the centers of which often exhibit cystic degeneration, so that there is at least a superficial resemblance to large follicles. This so-called von Kahliden type was therefore formerly often spoken of as folliculoma malignum. Still other variations occur, such as the gyriform and the pseudoadenomatous.

Grossly granulosa cell tumors may be of minute size or they may reach very large proportions. The smaller ones are apt to be solid, but those of larger size commonly show one or more cystic cavities due to liquefaction changes. The substance of the tumor, as revealed on cross section, is of grayish granular appearance with often areas of yellowish hue. The thecomas as a group are apt to be of more moderate size and of fibromatous appearance, although softer areas and small cystic cavities may likewise be noted.

There is much more difficulty in describing the pathology of arrhenoblastoma, which includes a whole series of gradations, from highly differentiated testicular tissue at one extreme to tumors so undifferentiated that only close study will reveal the sex cordlike cell arrangement that may constitute the only clue to their real nature. It is here that a knowledge of early gonadal embryology will stand the pathologist in good stead. Meyer has distinguished three varieties. The

highly differentiated type corresponds to the so-called testicular adenoma, originally described by Pick. Between this and the very undifferentiated variety falls the intermediate type, in which one always finds a tendency to tubule arrangement, representing abortive efforts at reproducing the testicular tubules. Other testicular characteristics, such as rete elements or groups of cells resembling the interstitial cells of Leydig, are found in a considerable proportion of cases.

Grossly the arrhenoblastoma is almost always a solid tumor of small or moderate size, although in some cases the growths have been very large, even to the size of a man's head. The cut surface is fairly firm and of grayish color, often with areas of yellowish tint, and sometimes of reddish, hemorrhagic appearance. As a result of secondary degenerative changes, cystic cavities of considerable size may be formed.

*Malignancy.*—The general statement may be made that while both granulosa cell carcinoma and arrhenoblastoma are undoubtedly much less malignant than the more common types of ovarian carcinoma, they are always to be looked upon as potentially malignant, and in many individual cases the degree of clinical malignancy is high. It is, of course, true that in many instances such neoplasms have seemed to run a benign course with no recurrence after unilateral removal of the adnexa. This has been particularly true in young children, perhaps because at this age the endocrine symptoms produced by such tumors are more striking than in later life, leading to their early recognition.

On the other hand, other members of this tumor group have been highly malignant, with rapid recurrence even after radical operations. Moreover, recurrence has sometimes been very late, after intervals of ten or even eighteen years. Only a few follow-up studies have been made, but I believe that the 28.1 per cent recurrence rate revealed in the series reported by Novak and Brawner would give a fair estimate of the degree of malignancy of the general group, although some authors put it much lower. In any event there does not seem any justification for the rather light attitude exhibited by some writers toward this type of tumor, especially since histologic criteria have not been found to constitute a reliable index of the degree of malignancy.

Still less certain are we as to the exact degree of malignancy of arrhenoblastoma. Only a few more than sixty cases have thus far been recorded, and most of these, because of the biologic interest of the tumors, have been reported soon after observation, too soon to permit of any statement as to the ultimate result. That they may recur after removal is shown in the cases of Novak and Long, Meyer, Kleinhans, von Szathmary and Taylor, and Wolfermann and Krock. On the other hand, as with granulosa cell carcinoma, a considerably larger group of patients has apparently been cured by conservative operations.

## ENDOCRINE EFFECTS

*Feminizing Group.*—Bearing in mind the estrogen-producing function of this group of tumors, it is easy to understand their biologic effects. The latter, as might be expected, will differ according to the age period at which such tumors develop.

When such growths arise in young children, as they sometimes do, their effects are what one would expect from the production of large amounts of estrogen long before the age of puberty. The characteristic secondary sex characteristics which appear normally at the pubertal epoch are due to the awakening estrogenic function which occurs at that time. When the organism is subjected to the estrogen stimulation of granulosa tumors abnormally early, one would expect evidences of precocious puberty, and this is exactly what occurs. Premature menstruation, premature hypertrophy of the breasts, and axillary and genital hairgrowth are the most conspicuous symptoms. The periodic bleeding is not associated with ovulation, in which respect it differs from that seen with precocious puberty due to certain extra-ovarian factors. Removal of the tumor is followed by prompt regression of the precocious symptoms, this constituting a clear-cut demonstration of the causal role of the tumor in the production of the syndrome.

During menstrual life, the ovaries normally produce considerable quantities of estrogen, and the secondary sex characters are already fully developed. The effects of estrogen-producing tumors in such women are therefore merely quantitative, the chief effects being on the menstrual function. Even these may not be notable, as we know that a relative hyperestrogenism is not invariably associated with menstrual excess. While the latter often occurs, menstruation may be quite normal or it may even be absent for many months at a time.

The uterus retains its sensitivity to estrogen long after the menopause, so that feminizing tumors in postmenopausal patients bring about varying degrees of increase in size of that organ above that of the usual senile uterus. Moreover, the uterine mucosa characteristically exhibits a hyperplasia, while periodic bleeding is likely to occur, simulating a re-establishment of menstruation. As in the prepubertal group, this is of the anovulatory, estrogen-induced type. The breasts of the senile women have lost their reactivity to estrogen, so that breast changes are not noted.

*Masculinizing Group.*—The production of androgenic principles by the masculinizing tumors brings about a sequence of endocrine effects which is divisible into two phases. The first of these consists in the appearance of certain symptoms which are not in themselves masculinizing but which represent a subtraction of certain features from the typically feminine complex. Among these symptoms are amenorrhea,

retrogression of the breasts, and sometimes a loss of the subcutaneous fat which gives the female figure its typical rounded contour. This defeminization phase is followed by the appearance of certain phenomena which are to be looked upon as definitely masculinizing. Chief among these are the appearance of a hairy growth on the face and other parts of the body, hypertrophy of the clitoris, and deepening of the voice. This is the sequence to be expected in the characteristic case, although there are all sorts of variations in degree.

As a matter of fact, there are some tumors which undoubtedly belong in this pathologic category but which produce little or no endocrine effect. In some cases this is explained by the very small size of the growths, while in other cases the explanation is uncertain and speculative. Removal of the tumor is followed by regression of the abnormal phenomena, although this is not always as complete and prompt as with the feminizing group. The defeminization phenomena disappear promptly and completely, but the genuinely masculinizing signs regress much more slowly and sometimes incompletely.

*Diagnosis.*—From what has been said it is evident that the preoperative diagnosis of granulosa cell carcinoma during menstrual life is rarely, if ever, possible, as it does not ordinarily give rise to symptoms different from other types of ovarian tumor. On the other hand, when an ovarian tumor is demonstrated in a child who exhibits the clinical phenomena of precocious puberty, it is reasonably certain to be of the granulosal type. It should not be forgotten, however, that certain other causes of precocious puberty are more frequent than this, and unless a tumor is palpable operation is not usually justified. That this is not an unnecessary admonition I know from personal knowledge of a number of cases in which ovaries have been removed merely on the suspicion that they may harbor small granulosa cell tumors. In patients of this early age group the demonstration of considerable quantities of estrogen in the urine would be suggestive but not conclusive, as the same finding might be noted in patients in whom an extraovarian factor is responsible for the precocious appearance of menstruation and other pubertal phenomena.

In the postmenopausal group, the association of periodic bleeding with an ovarian neoplasm, especially when the uterus is well above the senile size, should make one suspect granulosa cell carcinoma. Diagnostic curettage in such cases is likely to show a hyperplastic rather than atrophic endometrium. However, it is to be remembered that postmenopausal hyperplasia of the endometrium occasionally occurs in the entire absence of any tumor, just as estrogen may be found in the urine of some women long after the menopause. However, a judicious weighing of such evidence will permit of at least a strongly presumptive diagnosis in some cases.

As to arrhenoblastoma, the demonstration of a definite solid ovarian tumor in a woman previously normal and then developing defemini-

zation phenomena, followed soon by hirsutism, clitoris hypertrophy, and voice changes permits one to make a presumptive diagnosis of masculinizing tumor. This would usually prove to be arrhenoblastoma but rarely might be the adrenal type of ovarian tumor, which gives rise to identical symptoms. Here again a word of caution is necessary. The finding of a tumor in a woman who shows hypertrichosis, flat breasts, a rather deep voice, and perhaps amenorrhea does not justify any worth-while suspicion of arrhenoblastoma if the secondary sex abnormalities date from puberty, as they so often do. In such cases the evidences of mild intersexuality are almost always of the congenital or chromosomal type. Any associated ovarian tumor is likely, therefore, to be purely coincidental, and operation will usually reveal one of the ordinary tumor types, such as cystadenoma. When, however, the abnormal symptoms develop rather abruptly in women who previously have been typically feminine, the finding of an ovarian tumor is much more significant. Sex hormone studies have not yet proved of any great value as a help in the diagnosis of this group of tumors.

*Treatment.*—The treatment of the tumors of this entire group is surgical, but a word as to the extent of the operation seems necessary. Certainly in young individuals, in whom it is obviously highly important to preserve reproductive function, the operation should be a conservative one. In cases of this group, especially in children, the tumor is usually small and unilateral, and removal of the adnexa of the diseased side is ordinarily indicated. Postoperative radiotherapy would obviously be contraindicated, as in itself it might result in sterilization of the patient. The importance of postoperative follow-up need hardly be stressed in view of the potentialities of such tumors.

When such tumors are encountered in older women, as is true of the largest proportion, conservative operation would seem unwise. As a matter of fact, the real nature of granulosa cell carcinoma is often not suspected at the operating table, especially by the surgeon untrained in pathology. It is likely to be mistaken for ovarian carcinoma of the more ordinary types, so that complete removal of the uterus and adnexa is done, or should be done, whenever possible. While the results in the functioning group of tumors are in the main much better than with ovarian carcinoma in general, recurrences are sufficiently frequent to indicate the malignant potentialities of this entire group and to contraindicate any attempt at conservatism except under the conditions emphasized in the previous paragraph.

Opinions still differ as to the value of postoperative radiation where radical operation has been done, although most surgeons will probably prefer to employ this extra measure with these tumors as with other forms of malignant ovarian tumors. There are undoubtedly some members of this special tumor family, especially some cases of granu-



losa cell carcinoma, which are relatively radiosensitive, although even rapid recurrence may in other cases occur even if radical operation has been followed by radiation.

## REFERENCES

- Arnold, W., Koerner, J., and Mathias, E.: Zur Pathologie der Gewächse mit morphogenetischen Einflusung, *Virchows Arch. f. path. Anat.* 277: 48, 1930.
- Baldwin, L. G., and Gafford, J. A., Jr.: Arrhenoblastoma. Case Report, *Endocrinology* 20: 373, 1936.
- Bland, P. B., and Goldstein, L.: Granulosa Cell and Brenner Tumors of Ovary, *Surg., Gynec. & Obst.* 61: 250, 1935.
- Dworzak, H.: Ueber einen Fall von Granulosazelltumor, *Zentralbl. f. Gynäk.* 56: 1033, 1932.
- Emge, L.: Functional and Growth Characteristics of Struma Ovarii, *Am. J. Obst. & Gynec.* 40: 738, 1940.
- Geist, S. H.: Histogenesis of Certain Ovarian Tumors and Their Biologic Effects, *Am. J. Obst. & Gynec.* 30: 650, 1935.
- Greenhill, J. P., and Greenblatt, R. B.: Status of Thecoma and Its Relationship to Granulosa Cell Tumor, *Am. J. Obst. & Gynec.* 36: 684, 1938.
- Melnick, P. F., and Kantner, A. E.: Theca Cell Tumors of the Ovary, *Am. J. Obst. & Gynec.* 27: 41, 1934.
- Meyer, R.: Pathology of Some Special Ovarian Tumors and Relation to Sex Characteristics, *Am. J. Obst. & Gynec.* 26: 505, 1933. (This article contains references to previous papers by this author: Über Adenoma malignum ovarii, *Ztschr. f. Geburtsh. u. Gynäk.* 76: 616, 1915; Tubuläre [testikuläre] und solide Formen des Andreioblastoma ovarii, *Beitr. z. path. Anat. u. z. allg. Path.* 84: 485, 1930.)
- Novak, E.: Masculinizing Tumors of the Ovary (Arrhenoblastoma; Adrenal Ovarian Tumors), *Am. J. Obst. & Gynec.* 36: 840, 1938.
- Idem: Granulosa Cell Ovarian Tumors as Cause of Precocious Puberty, With Report of 3 Cases, *Am. J. Obst. & Gynec.* 26: 505, 1933.
- Idem: Granulosa Cell Carcinoma of Ovary as Cause of Postmenopausal Bleeding, *Am. J. Surg.* 24: 595, 1934.
- Novak, E., and Brawner, J. N.: Granulosa Cell Tumors of the Ovary. Clinical and Pathological Study of 36 Cases, *Am. J. Obst. & Gynec.* 28: 637, 1934.
- Novak, E., and Gray, L. A.: Clinical and Pathological Differentiation of Certain Special Ovarian Tumors, *Am. J. Obst. & Gynec.* 31: 213, 1936.
- Idem: Dysgerminoma of Ovary, *Am. J. Obst. & Gynec.* 35: 925, 1938.
- Novak, E., and Long, J. H.: Ovarian Tumors Associated With Secondary Sex Changes, *J. A. M. A.* 101: 1057, 1933.
- Pick, L.: Über Adenome der männlichen und weiblichen Keimdrüse, *Berl. klin. therap. Wchnschr.* 42: 502, 1905.
- Rottino, A., and McGrath, J. F.: Masculinovoblastoma, Primary Masculinizing Tumor of Ovary (So-Called Large Cell Variety-Hypernephroid-Luteoma), *Arch. Int. Med.* 63: 686, 1939.
- Schiller, W.: Zur Frage der Spezifität vermännlichender Ovarialtumoren, *Arch. f. Gynäk.* 160: 344, 1933.
- Idem: Pathologie und Klinik der Granulosazelltumoren, Wien, 1934. Wilhelm Maudrich.
- Schulze, M.: Granulosa Cell Tumors of Ovary, *Am. J. Obst. & Gynec.* 26: 627, 1933.
- Schuschania, P.: Ergebnisse von Mengenbestimmungen des Sexualhormons; Sexualhormon im Harn und Kot bei (a) Metropathia hemorrhagica juvenilis (glandular-cystischen Hyperplasie); (b) Granulosazelltumor des Ovars mit glandular-cystischer Hyperplasie des Endometriums, *Zentralbl. f. Gynäk.* 54: 1924, 1930.
- Taylor, J. M., Wolfertman, S. J., and Krock, F.: Arrhenoblastoma of Ovary, *Surg., Gynec. & Obst.* 56: 1040, 1933.
- Te Linde, R. W., and Henriksen, E.: Decidua-Like Changes in Endometrium Without Pregnancy, *Am. J. Obst. & Gynec.* 39: 733, 1940.

## ENDOCRINE FACTORS IN THE ORIGIN OF TUMORS OF THE UTERUS

HOWARD C. TAYLOR, JR., M.D., NEW YORK, N. Y.

**T**HEORIES on the causes of all tumors, perhaps especially those of the reproductive organs, have undergone a radical revision in the last ten or fifteen years. Prior to that time chief emphasis was placed upon trauma or chronic irritation with the hypothesis of the special predisposition of displaced embryonal rests to be used when other explanations were lacking. Carcinoma of the cervix was generally regarded as arising on the basis of chronic inflammatory lesions developing in lacerations sustained during childbirth. Cancer of the breast was assigned sometimes to trauma, sometimes to the irritating effects of undischarged secretion. Cancer of the endometrium was given little consideration but was somewhat loosely referred to senile endometritis. The embryonal theory on the other hand was of value in explaining certain complicated new growths, especially of the adenomyoma group, but fibroids and some ovarian tumors were also often laid to the persistence and late development of various embryonic structures. These factors are not yet to be excluded, but they have been relegated to the background to give place to the study of specific chemical stimuli, particularly those of hormonal character.

Although recent progress toward the establishment of the hormones as a factor in tumor genesis has been chiefly in the hands of laboratory workers, it must not be supposed that their work was the actual beginning. Intimations that endocrine factors were concerned in the origin of pelvic tumors date relatively far back in modern gynecologic history. Sixty years ago Brennecke<sup>6</sup> recognized a hyperplastic condition of the endometrium and correctly ascribed it to disturbances in ovulation and corpus luteum formation, a point amply confirmed and widely accepted by gynecologists many years before the hormones of the ovary had been isolated. The relationship of the uterine fibromyoma to the ovary has also been carefully considered by several generations of clinical gynecologists and since Hegar's<sup>29</sup> article of 1887, there has been an almost unbroken series of reported observations on the nature of the ovarian lesion associated with this tumor.

The experimental period in the investigation of these relationships was initiated by several fundamental discoveries in the fields of biology and chemistry. Of primary importance was the Allen-Doisy test which made possible the measurements of estrogenic activity. Of equal value was the isolation and eventual synthesis of many of the sex

hormones in pure form. With these instruments for research and the successful breeding of strains of mice with a hereditary cancer of the mammary gland, the development of a new field in the investigation of reproductory tract tumors was ready to commence.

Work on the experimental production of animal tumors by means of hormones has produced a great body of literature which has been adequately reviewed elsewhere.<sup>2, 19, 78</sup> As a result of these investigations a number of neoplasms are now readily produced in several species of animals which are similar in their microscopic structure to many of the common spontaneously occurring human tumors. Perhaps the principal problem of the moment is to find satisfactory evidence that in women with tumors of these types hormone conditions have been present which in some way resemble those that must be artificially created to produce the experimental tumors in animals.

Methods of studying ovarian function in human beings are still imperfect and clinical evidence of a hormone disorder associated with a developing tumor is indirect and difficult to evaluate. Briefly such evidence may be classified under several headings.

1. The clinical history has for years led to inferences in regard to the origin of tumors. The relation to previous pregnancies or to sterility, records of past menstrual disturbances or of anomalies of puberty or the menopause are all data which can be statistically handled and must be taken into account.

2. Histologic or pathologic study of various parts of the reproductive organs may yield information of value. The ovaries themselves may contain follicle cysts or a granulosa cell tumor as an acceptable source of the estrogens which produced the tumor. The endometrium on the other hand may be looked upon as a sensitive indicator of sex endocrine function and its status in a patient with a reproductive tract tumor will indicate whether, at the moment at least, the ovarian function is normal. Finally a tendency to the association of several tumors in the reproductive tract of the same individual is of interest, for it indicates either a general predisposition or a type of stimulus having a widespread effectiveness, as might be expected from a hormone as a factor in tumor development.

3. Clinical therapy has made some contributions to the solution of the problem. The fact that many of the benign reproductory tract tumors tended to shrink or even disappear after bilateral oophorectomy has long been known and accepted as proof that substances formed in the ovary were, if not the cause of the tumor, at least essential in maintaining the continued susceptibility of the organs to tumor formation. More recently there have been some reports indicating that the administration of various hormone substances, the estrogens, progesterone or testosterone, might accelerate or modify the growth of neoplasms in the female pelvic organs.

4. Finally, evidence to solve this problem has been sought in the excretion rates of various products of the sex endocrine organs. These studies have been interesting but have led to limited conclusions. The rate of urinary excretion of an estrogen, for example, may have a very remote relationship to its rate of formation or of its utilization by specific tissues. Nor does the estrogen excretion in a patient with a fully developed tumor give much indication of the conditions under which tumor growth was initiated, perhaps years before.

Evidence such as this is all that is available to the clinician to check the suggestions made to him by the animal experimenter. In the following pages the principal tumors produced by hormonal agents in the uterus of various laboratory animals will be considered in relation to the morphologically similar tumors in women and the reasons given for believing that the causes of these tumors may also be similar.

*Endometrial Hyperplasia.*—Hyperplasia of the endometrium has become a clinical entity accepted by most gynecologists. The histologic picture, with the glands of irregular size lined by nonsecreting epithelium, is fairly characteristic although extreme forms may range from those which are difficult to distinguish from normal proliferating endometrium on the one hand to those suggestive of early adenocarcinoma on the other.

The typical histologic pattern of endometrial hyperplasia has been produced in all of the common laboratory animals by the simple injection of various estrogenic compounds.<sup>8, 85-87, 89</sup> Evidence is accumulating, however, that a great excess in estrogenic stimulation is not the essential factor in the cause of the disease, but rather a continuity of estrogenic stimulation without the periods of rest afforded by the normal estrus cycle. The development of the disease is also favored by the absence of the usual balancing effect of the corpus luteum. The relationship of endometrial hyperplasia to disturbed rather than simple excessive ovarian function is made especially evident by studies of Lipschütz<sup>42, 43</sup> on the effect of partial oophorectomy in the guinea pig. He found that an imbalance resulted when the residual fragment of ovary underwent a compensatory hypertrophy of the follicles with incomplete or absent corpus luteum development, and in animals so treated there developed numerous signs of atypical tissue proliferations among which hyperplasia of the endometrium was prominent. Hyperplasia has also been reported to follow the disturbances of ovarian function resulting from the irradiation of the ovaries by x-rays<sup>69</sup> and by the implantation of testicular tissue.<sup>63</sup> The protective effect of the corpus luteum is shown by the reports of several writers that hyperplasia is more difficult to produce by means of an estrogen if the animal's own ovaries are not first removed<sup>53</sup> or if progesterone is simultaneously administered.<sup>55</sup>

The evidence that hyperplasia of the endometrium as it occurs in women has the same cause as the experimentally produced animal lesion is quite convincing. Schroeder,<sup>70</sup> in 1915, published his work ascribing the disease to the persistence and prolonged action of an unruptured Graafian follicle on the endometrium, basing his theory on a series of cases in which he found a large follicle in the ovary and no recent corpus luteum. The condition of the ovaries in cases of hyperplasia has been the object of numerous investigations since that time, all tending to confirm the view that the disease results from prolonged follicular activity without normal corpus luteum formation.

Interesting support of this relationship is found in cases of certain ovarian tumors. Both granulosa- and theca-cell tumors of the ovary manufacture estrogenic material which can be detected in the urine in large quantities. As is well known, uterine bleeding from a hyperplastic endometrium is a common symptom of this type of tumor.

Efforts to demonstrate excessive quantities of estrogenic substance in the urine of patients with this disease have in general indicated an increased excretion of the hormone.<sup>16, 29, 74, 83</sup> Investigations on this subject were carried on during the earlier days of urinary hormone studies, however, and there appears to be a real opportunity for detailed study of steroid excretion in such cases with the utilization of more modern techniques.

The observed effects of treatment also tend to confirm the endocrine nature of this disease. Castration is invariably curative, a fact which makes very successful the radium or x-ray treatment of women with benign vaginal bleeding at the time of the menopause. Furthermore, the administration of very large doses of an estrogen, 600,000 international units, may be followed by the production of an experimental hyperplasia in women, histologically similar to the spontaneous disease.<sup>87</sup> Consistent with the previously noted facts on the etiology of the disease is the observation that progesterone in large doses has a curative effect.<sup>72</sup>

One somewhat confusing point has arisen with the observation of cases of hyperplasia developing some years after the menopause.<sup>5, 57, 80</sup> Various hypotheses have been offered as to the source of the estrogens which might produce the lesion late in life. At present the estrogenic origin of the proliferative changes in the senile endometrium must be held in some doubt.

The origin of the cystic hyperplasia of the human endometrium on the basis of a dysfunction of the ovary, resulting in what may be characterized as a persistent, unopposed action of estrogen, may be regarded as established. This being true, the finding of endometrial hyperplasia in association with another reproductive tract tumor is at least presumptive evidence that the estrogens play some part in the origin of the other tumor also. This reasoning has been used to relate a considerable list of pelvic tumors to an ovarian hyperfunction.

*Squamous Metaplasia of the Endometrium.*—In a number of animal experiments the transformation of portions of the endometrium into a stratified squamous epithelium has been reported as an estrogen effect.<sup>40, 48, 53</sup> Lipschütz<sup>53</sup> also observed this in guinea pigs after partial oophorectomy.

Islands of squamous epithelium are well known to occur in the human endometrium (Fig. 1) and are perhaps the counterpart of the squamous metaplasia developing in animals after estrogens. Such metaplasia is a not uncommon associated finding in cases of endometrial hyperplasia,<sup>33</sup> a point giving a little support to the estrogenic view of its origin.



Fig. 1.—Squamous metaplasia of the endometrium with adenocarcinoma.

*Carcinoma of the Endometrium.*—Although no tissue would appear to be more susceptible to the action of the estrogens, tumors of the endometrium have rarely been reported in laboratory animals after estrogen injections. Those which have developed seem to have only a remote morphologic relationship to the carcinoma of the corpus uteri in women.<sup>41, 64</sup>

Spontaneously developing tumors of the rabbit endometrium have, however, been described and arise under circumstances which give a new direction to thought on the nature of the endocrine factor in carcinogenesis. These “adenomata” arise multicentrically in the glandular mucosa of relatively old animals and spread by both local extension and metastasis.<sup>27</sup> Their appearance is associated with certain changes in the adrenals, thyroid, ovaries, and mammary glands which are some-

what similar to the effects produced by estrogen injection. Of particular interest was Greene's observation that tumors occurred in animals that had previously suffered from mild attacks of "toxemia of pregnancy," which he felt may have caused damage to the liver and a relative incapacity to inactivate estrogens.<sup>26</sup> This mechanism, if correct, would implicate the liver as a possible cause of many excessive estrogen effects.

The evidence for an estrogenic factor in the origin of endometrial cancer in women is confusing. From a clinical standpoint, it is noteworthy that the disease has a slight tendency to favor nulliparous women and it has been reported to have a special predilection for women with a delayed menopause.<sup>9</sup> Both of these trends suggest an endocrine factor.

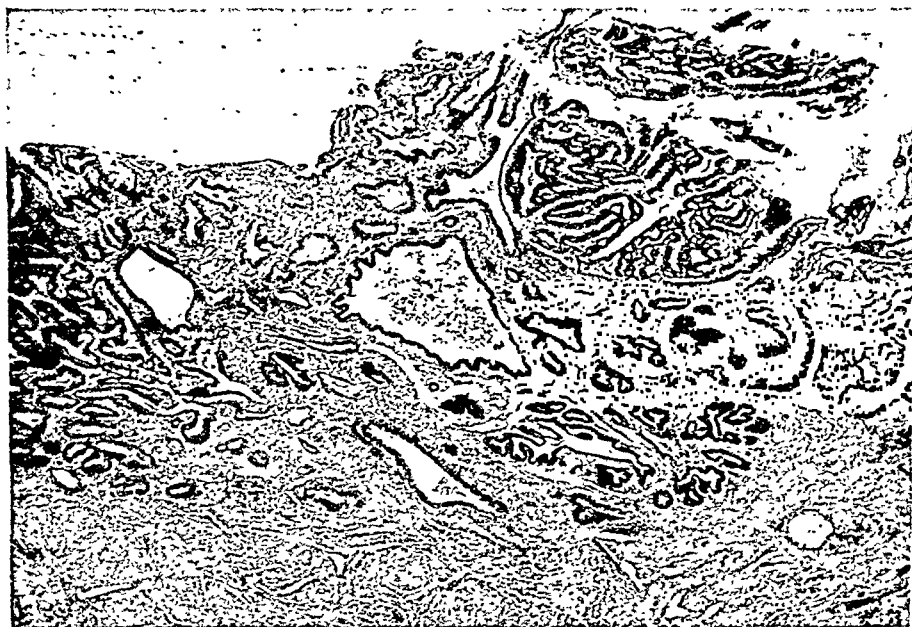


Fig. 2.—Adenocarcinoma associated with hyperplasia of the endometrium in a patient 48 years of age.

The relationship of carcinoma to hyperplasia of the endometrium is an important and disputed point. Certainly only a very small proportion of the cases of the very common hyperplastic lesion can go on to develop into the relatively rare cancer of the corpus uteri. Follow-up studies of cases of endometrial hyperplasia have in fact yielded few examples of later development of cancer.<sup>34, 49</sup>

Pathologic specimens in which carcinoma is found arising in a hyperplastic endometrium are not uncommon according to certain observers,<sup>58, 77</sup> whereas others insist that the association is no more than accidental.<sup>15, 38, 62</sup> Herrell<sup>31</sup> denies that hyperplasia is commonly found

with corpus carcinoma, but notes instead that in 96 per cent of the 50 cases he studied there was a "persistent proliferative type of endometrium." This he regarded as due to the "unopposed action of the follicular hormone." Jones and Brewer,<sup>38</sup> in a study of 68 patients with corpus cancer, found only 2 with cystic hyperplasia and concluded that there was no evidence for the "unopposed action" of estrin in the production of endometrial cancer. These wide differences of opinion must evidently be due in part to a lack of agreement as to what constitutes hyperplasia of the endometrium in the postmenopausal woman, the type of patient in which cancer of the endometrium usually occurs.

An example of the association of hyperplasia and adenocarcinoma of the uterus is shown in Fig. 2. It is of interest that in this case another lesion, in which an estrogenic factor must likewise be considered, namely, adenomyosis of the uterus, was also present (Fig. 3).



Fig. 3.—Adenocarcinoma associated with adenomyosis in the patient shown in Fig. 2.

While this controversy continues, another group of cases is beginning to be reported which may constitute the most important evidence for an estrogen factor in endometrial cancer. These belong to the steadily increasing list of patients who have been observed with an association of a granulosa cell tumor of the ovary with an adenocarcinoma of the endometrium. Apparently the first of these was described by Schroeder,<sup>71</sup> in 1922, but recently there have been reports of several, notably 3 by Dockerty,<sup>11</sup> 3 by Stohr,<sup>75</sup> 1 by Russell,<sup>67</sup> and 1 by Taylor and Greeley.<sup>79</sup> Another possibly similar case has recently been observed at the Memorial Hospital and is illustrated in Figs. 4 and 5. Two cases are also on record of carcinoma of the endometrium in association with theca-cell tumors of the ovary.<sup>11, 66</sup> In view of the relative



rarity of these ovarian tumors it is scarcely conceivable that the association with endometrial cancer was mere accident. With the estrin-producing capacity of the granulosa-cell and theca-cell tumors in mind, it is difficult to deny the probable sequence of hyperestrinism, hyper-

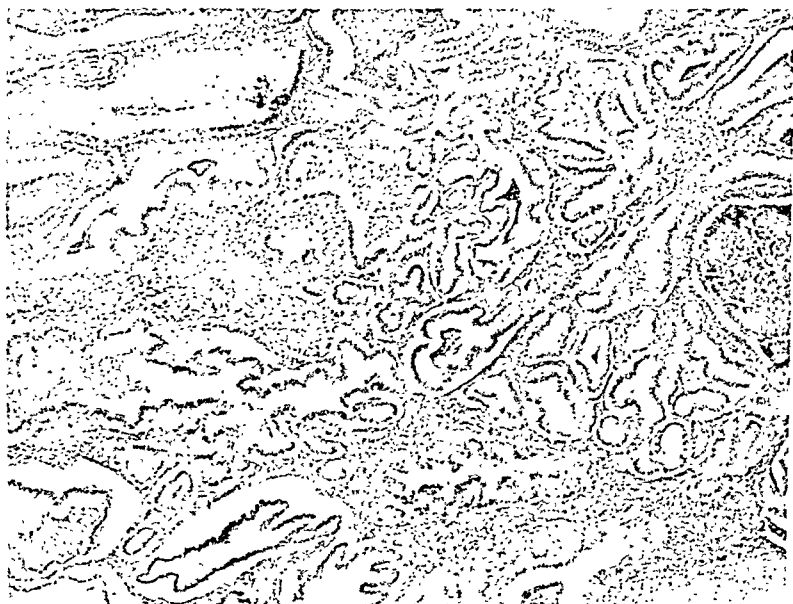


Fig. 4.—Adenocarcinoma or hyperplasia of endometrium in uterus of 65-year-old woman with granulosa-cell tumor.

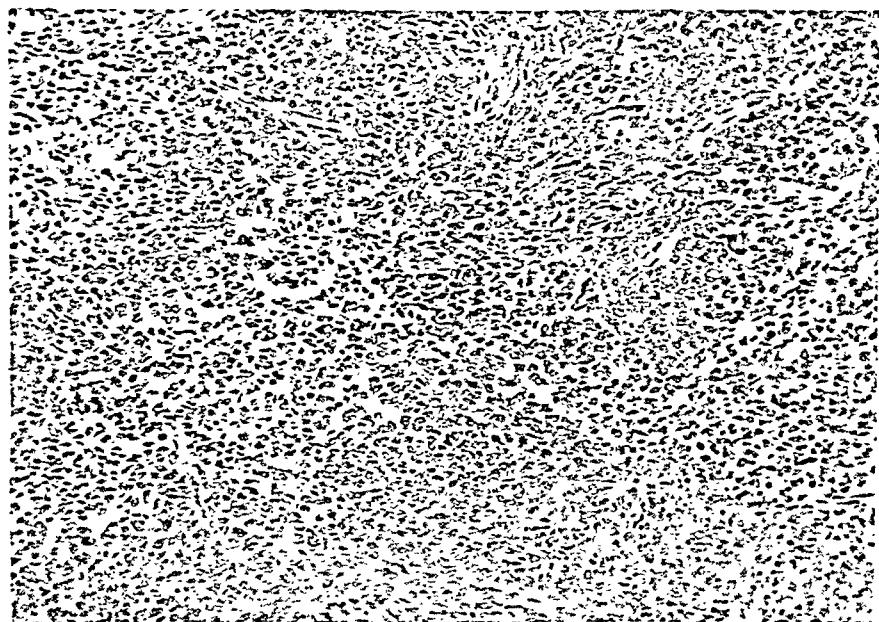


Fig. 5.—Granulosa-cell tumor in patient whose endometrium is shown in Fig. 4.

plasia of the senile endometrium, and cancer in at least this special group.

*Fibromyoma Uteri*.—The attempts to produce tumors of the smooth muscle of the uterus illustrate very well the presence of factors of susceptibility inherent in the species, race, or individual in addition to some precipitating cause such as an endocrine stimulus. The prodigious number of mice, rats, and rabbits injected with various estrogens failed to yield any convincing myomas of the uterus. Injections of estrogens into guinea pigs led immediately to fibromatous tumors, not only of the myometrium but of subperitoneal tissues throughout the abdominal cavity. Although the production of these tumors was first reported by Nelson,<sup>54</sup> the detailed study of these growths and the special conditions underlying their appearance have been made by Lipschütz and his co-workers in Chile.<sup>44-47</sup>

The estrogen-produced tumors of the guinea pig are fibromas with some smooth muscle fibers, arising perhaps by proliferation of the ectomic endothelium.<sup>47</sup> Tumors appear on the uterus, but also on the surface of the liver, stomach, intestine, parietal peritoneum, and under-surface of the diaphragm.<sup>44</sup> Various estrogens will result in these tumors but an esterified compound, such as estradiol benzoate, appears to be the most effective, perhaps because with this the estrogen effect is most continuous. Discontinuous treatments, even if carried on over a long period of time and with large doses, may fail to produce tumors,<sup>45</sup> and their appearance may be prevented by combining progesterone or testosterone propionate with the estrogen injections.<sup>46</sup> The conditions governing the production of these tumors follow the rule noted before for hyperplasia of the endometrium, namely, that stimulation should be continuous and not balanced by the moderating effect of the corpus luteum.

Corroborating evidence that the fibromyomas in the human being are due to the estrogens is diverse and controversial. Pathologic changes in the ovaries of women with fibroids have been discussed for at least fifty years with little progress being made, perhaps because of our meager knowledge of the morphologic basis of ovarian dysfunctions. In recent years Witherspoon<sup>82</sup> particularly has stressed the association of follicular cysts with fibroids and on the basis of his observations has built up a theory of hyperestrinism as the cause of these tumors. Two very careful studies<sup>7, 28</sup> deny that cystic changes occur with any unusual frequency. Brewer and Jones<sup>7</sup> in particular have recently studied the ovaries in a series of 100 patients with fibromyoma and report that ovulation and corpus luteum formation were found in the frequency to be expected in normal women.

The disagreement as to the endometrial patterns in patients with fibroids parallels that in regard to the state of the ovaries. Witherspoon<sup>82</sup> found that hyperplasia of the endometrium was frequently

associated with uterine fibroids and reported a series of 44 women originally found to have only endometrial hyperplasia who subsequently developed fibroids. He believed that hyperestrinism was the common cause of hyperplasia of the endometrium and of fibroids, the former developing when the causative factors were operative over a short period, the latter when over a longer period. Against this extreme view may again be cited the work of Brewer and Jones<sup>7</sup> who in their series of 100 fibroids found only one example of hyperplasia and that of moderate degree.

A particular opponent of an ovarian dysfunction as the cause of fibroids is Robert Meyer,<sup>51</sup> who pointed out that many women with fibroids undergo normal cyclical changes in the endometrium, menstruate regularly, and even become pregnant. Some dependence upon the ovary is of course evident because of the shrinkage in the size of the tumor after the menopause. This may occur through the intermediation of the blood supply, however, and fibroids with extensive vascular adhesions to extra pelvic abdominal organs may continue to grow after the menopause in spite of atrophy of ovaries and uterus.<sup>50</sup>

More direct studies of the estrogens in relation to fibroid growth in women have met with little success. High concentrations of estrogenic substances in the tumors themselves have been reported, but these observations are now largely discredited. The excretion of estrogenic and androgenic substances in the urine of women with fibroids appears to be normal.<sup>18</sup>

The case for a hormone factor in the etiology of fibroids in women still seems to rest chiefly on the atrophy that undoubtedly results from removal or destruction of ovarian function. To this may perhaps be added the support afforded by the experimental production of allied, but perhaps not strictly analogous, tumors in the guinea pig.

*Adenomyosis Uteri.*—The active penetration of the myometrium by glands from the basal layers of the endometrium is another lesion which apparently develops only during years of active ovarian function. Formerly regarded as inflammatory and termed adenomyositis, it has gradually come to be regarded as in some sense an endocrine induced disease, resulting either from a lost resistance of the endometrium or an increased capacity for regeneration of the basal layers.<sup>52</sup>

Experimental production of adenomyosis has been little considered, perhaps because the preclinical workers are scarcely conscious of the lesion. Penetration of the muscularis by endometrial glands has been observed after estrogens, however, and is beautifully illustrated in the work of Lipschütz in which he produced various types of genital hyperplasia in guinea pigs by partial oophorectomy.<sup>43</sup> The only clinical evidence that has been offered for the ovarian origin of adenomyosis of the uterine wall has been that afforded by the association of other lesions, in particular pathologic changes in the ovaries,<sup>1, 37</sup> granulosa-cell tumor of the ovary,<sup>51</sup> and hyperplasia of the endometrium.<sup>37, 56</sup>

The patient, microphotographs of whose uterus are shown in Figs. 2 and 3, is illustrative of this point.

*Squamous Metaplasia and Precancerous Lesions of the Cervix.*—Transformation of the columnar cells of the cervix into a stratified squamous epithelium is a commonly observed sequel to estrogen injections in many animal species. The first report on the production of such lesions in the monkey was made by Overholser and Allen<sup>60</sup> who at first believed that the lesion produced was actually beginning carcinoma, but subsequent work has shown that these estrogen-produced lesions of the cervix in the monkey and most animal species are not malignant.<sup>12, 50, 55, 61, 88</sup> The structures produced do, however, closely resemble lesions familiar to the gynecologist as leucoplakia and squamous metaplasia or epidermidalization of the cervical glands.



Fig. 6.—Squamous metaplasia of columnar epithelium in a cervical polyp.

Evidence from human material that such lesions are estrogenic in origin is largely lacking. Squamous metaplasia of the cervix has been reported in cases of granulosa-cell tumors and with hyperplasia of the endometrium,<sup>78</sup> but the frequency of this cervical lesion makes the significance of such association very slight. Squamous metaplasia is of course common in cervical polyps (Fig. 6) but here especially trauma and chronic infection appear to be important predisposing factors.

*Cancer of the Cervix.*—Until very recently it was more or less accepted that cancer of the cervix was due to the chronic irritation subsequent to the injuries of parturition or to chronic cervicitis. A few new facts have recently been brought to light which somewhat shake the dogmatic foundations of the inflammatory theor

Malignant tumors in mice receiving estrogens have now been produced in some numbers.<sup>20, 21</sup> These tumors are histologically cancer and have the qualities of local infiltration of the tissues of the rectal wall and bladder and of metastasis to the regional lymph nodes. The simultaneous administration of androgens did not prevent the appearance of cancer of the cervix in these animals.

Efforts are also being made to introduce the sex hormones into the background of human cervical cancer. Hofbauer<sup>36</sup> some years ago suggested that the well-known predilection of cancer of the cervix for multiparas was to be explained, not on the basis of the injuries of delivery, but upon the nine months of excessive hormone stimulation to which the cervix is subjected in each pregnancy. In substantiation



Fig. 7.—Early cancer of the cervix with superficial extension.

of this theory he offered the evidence of hyperplastic changes in the histologic sections from the cervixes of pregnant women. These views have received some support from the pathologic studies of Schiller,<sup>68</sup> Hinselmann,<sup>32</sup> and others which have shown that lesions of the cervix regarded as precancerous are not necessarily found in areas of cervicitis or cervical erosion, but on the contrary may appear in the midst of apparently normal epithelium (Fig. 7).

Cancer of the cervix in women does not appear to have any tendency to be associated with other lesions to which an estrogenic causative factor has been theoretically described. Uterine carcinoma associated with breast cancer is apt to be endometrial.<sup>77</sup> Myomas of the uterus seem more often to be associated with corpus than with cervical cancer

in relation to the relative frequency of the two latter conditions.<sup>4, 17, 50, 51</sup> Cervical cancer has not furthermore been reported, to my knowledge, with granulosa-cell tumors, nor has it even been stated that it had any tendency to occur with endometrial hyperplasia.

The excretion of abnormal hormone substances in the urine of patients with cervical cancer has been claimed. Increased excretion of gonadotropic substance was at one time reported, but it has never been clear that this observation was not the result of failure to distinguish the effect of the menopause on gonadotropic substance secretion.<sup>52</sup> Several early workers also reported excessive estrogen excretion, but these observations were based on methods that now must be regarded as quite inadequate. Very recently work has been reported, which still requires confirmation, that women with uterine cancer have abnormal urinary estrone: estriol ratios.<sup>65</sup>

It is interesting, finally, to note that the extensive use of estrogen therapy appears not to have led to any general conviction that the estrogens produce cervical cancer. A report of Gemmell and Jeffcoate<sup>21</sup> in which 3 patients out of 43 treated by estrogens for senile vaginitis and kraurosis vulvae developed cervical cancer is a single report which indicates that caution may be necessary. Geist and Salmon,<sup>22</sup> on the other hand, after treating 206 women for one-half to five and one-half years with total dosages of 500,000 to 23,400,000 international units, noted only regenerative effects and no signs of atypical or excessive proliferation.

#### CONCLUSION

In attempting to evaluate these diverse observations, a few points become clear. In animals the administration of various hormones, but particularly the estrogens, has been followed by the appearance of neoplasms throughout the reproductive tract. Various species of animals differ greatly in their susceptibility to develop tumors of a certain kind in response to these types of stimuli.

In women tumors morphologically similar to those appearing in animals after estrogen administration develop spontaneously. The benign tumors of this group are pretty sharply limited to the years of ovarian function for their active growth and tend to atrophy after the menopause. In this respect, at least, the ovary is a necessary factor in their development.

Evidence that a specific ovarian dysfunction is the cause is almost complete for certain types of hyperplasia of the endometrium. For the other neoplasias or tumors of the uterus the proof is very incomplete and rests on such indirect evidence as the observed conditions of the ovaries, the association of several tumors in the same patients, and the effects of treatment.

A better understanding of ovarian morphology and of the processes involved in the metabolism of the steroids is required before the hy-

potheses raised by the results of animal experiments can be finally proved for the origin of these reproductive tract tumors in man.

## REFERENCES

1. Adler: Fall von Schleimhautadenomyosis, *Zentralbl. f. Gynäk.* 49: 658, 1925.
2. Allen, E.: Ovarian Hormones and Female Genital Cancer, *J. A. M. A.* 114: 2107, 1940.
3. Allen, E., and Gardner, W. U.: Cancer of the Cervix of the Uterus in Hybrid Mice Following Long-Continued Administration of Estrogen, *Cancer Research* 1: 359, 1941.
4. Bowers, D. D.: Cancer and Fibromyomas of the Uterus, *Am. J. Obst. & Gynec.* 39: 830-836, 1940.
5. Breipohl, W.: Schleimhautbilder in der Menopause, *Zentralbl. f. Gynäk.* 59: 1998, 1935.
6. Brennecke: Zur Aetiologie der "Endometritis fungosa," speciell der "chronischen hyperplasirenden Endometritis Oldhausen's," *Arch. f. Gynäk.* 20: 455, 1882.
7. Brewer, J. I., and Jones, H. O.: A Study of the Corpora Lutea and the Endometrium in Patients With Uterine Fibroids, *Am. J. Obst. & Gynec.* 41: 733, 1941.
8. Burch, J. C., Williams, W. L., and Cunningham, R. S.: The Etiology of Endometrial Hyperplasia, *Surg., Gynec. & Obst.* 53: 338, 1931.
9. Crossen, R. J., and Hobbs, J. E.: Relationship of Late Menstruation to Carcinoma of the Corpus Uteri, *J. Missouri M. A.* 32: 361, 1935.
10. Dichtl, Peter: Über excessives Wachstum von Myomen jenseits des Klimakteriums, München, 1922, Inaug. Dissert.
11. Dockerty, M. B.: Theca Cell Tumors of the Ovary, *Am. J. Obst. & Gynec.* 39: 434, 1940.
12. Engle, E. T., and Smith, P. E.: Some Uterine Effects Obtained in Female Monkeys During Continued Oestrin Administration, *Anat. Rec.* 61: 471, 1935.
13. Fluhmann, C. F.: Epidermalization of the Cervix Uteri and Its Relation to Malignancy, *Am. J. Obst. & Gynec.* 15: 1, 1928.
14. Fluhmann, C. F.: Hyperplasia of the Endometrium and the Hormones of the Anterior Hypophysis and the Ovaries, *Surg., Gynec. & Obst.* 52: 1051, 1931.
15. Fluhmann, C. F., and Stephenson, H. A.: The Coincidence of Hyperplasia Endometrii and Carcinoma Corpus Uteri, *Surg., Gynec. & Obst.* 48: 425, 1929.
16. Frank, R. T., Goldberger, M. A., and Spielman, F.: Present Endocrine Diagnosis and Therapy, *J. A. M. A.* 103: 393, 1934.
17. Frankl, O.: Über Koinzidenz und Interferenz von Uterustumoren. II. Myom und Carcinom, *Arch. f. Gynäk.* 123: 1, 1924.
18. Furuhjelm, M.: On the Excretion of Oestrogenic and Androgenic Substances in the Urine of Women, *Acta obst. et gynec. Scandinav. (Supp. 1)* 20: 1-91, 1940.
19. Gardner, W. U.: Estrogens in Carcinogenesis, *Arch. Path.* 27: 138, 1939.
20. Gardner, W. U., and Allen, E.: Malignant and Non-Malignant Uterine and Vaginal Lesions in Mice Receiving Estrogens and Estrogens and Androgens Simultaneously, *Yale J. Biol. & Med.* 12: 213, 1939.
21. Gardner, W. U., Allen, E., Smith, G. M., and Strong, L. C.: Carcinoma of the Cervix of Mice Receiving Estrogens, *J. A. M. A.* 110: 1182, 1938.
22. Geist, S. H., and Salmon, U. J.: Are Estrogens Carcinogenic in the Human Female? The Effect of Long-Continued Estrogen Administration Upon the Uterine and Vaginal Mucosa of the Human Female, *Am. J. Obst. & Gynec.* 41: 29, 1941.
23. Gemmell, A. A., and Jeffcoate, T. N. A.: Oestrogens and Carcinoma of the Uterus, *J. Obst. & Gynaec. Brit. Emp.* 46: 985, 1939.
24. Greene, H. S. N.: Toxemia of Pregnancy in the Rabbit. I. Manifestations and Pathology, *J. Exper. Med.* 65: 809, 1937.
25. Greene, H. S. N.: Toxemia of Pregnancy in the Rabbit. II. Etiological Considerations With Especial Reference to Hereditary Factors, *J. Exper. Med.* 67: 369, 1938.
26. Greene, H. S. N.: Uterine Adenomata in the Rabbit. III. Susceptibility as a Function of Constitutional Factors, *J. Exper. Med.* 73: 273, 1941.
27. Greene, H. S. N., and Saxton, J. A., Jr.: Uterine Adenomata in the Rabbit. I. Clinical History, Pathology and Preliminary Transplantation Experiments, *J. Exper. Med.* 67: 691, 1938.

28. Hüggeström, P.: Ovarium und Endometrium bei Myomkranken, *Ztschr. f. Geburtsh. u. Gynäk.* 102: 36, 1932.
29. Hegar, A.: Zur Begriffsbestimmung der Kastration, *Centralbl. f. Gynäk.* 11: 698, 1887.
30. Herold, L., and Effkemann, G.: Zur Frage der Epithelmetaplasie der Cervix- und Korpusschleimhaut nach Zufuhr von Follikelhormon bei nichtkastrierten und kastrierten Ratten, *Zentralbl. f. Gynäk.* 61: 27, 1937.
31. Herrell, W. E.: Studies on the Endometrium in Association With the Normal Menstrual Cycle, With Ovarian Dysfunction and Cancer of the Uterus, *Am. J. Obst. & Gynec.* 37: 559, 1939.
32. Hinselmann, H.: Die Ätiologie, Symptomatologie und Diagnostik des Uteruscarcinoms, In: *Handbuch der Gynäkologie (Stoeckel)*, v. 6, pt. 1, München, 1930, J. F. Bergmann, p. 854.
33. Hintze, O.: Plattenepithelknötchen in hyperplastischen Drüsen der Korpusschleimhaut, *Zentralbl. f. Gynäk.* 52: 2209, 1928.
34. Hintze, O.: Klinische Nachuntersuchung an 24 Fällen schwerer Hyperplasie der Korpusschleimhaut, *Zentralbl. f. Gynäk.* 53: 2396, 1929.
35. Hisaw, F. L., and Lendrum, F. C.: Squamous Metaplasia in the Cervical Glands of the Monkey Following Oestrin Administration, *Endocrinology* 20: 228, 1936.
36. Hoffbauer, J.: Graviditätsveränderungen des Cervixepithels und ihre Stellung in der Ätiologie des Uteruskarzinoms, *Zentralbl. f. Gynäk.* 55: 428, 1931.
37. Jeffcoate, T. N. A., and Potter, A. L.: Endometriosis as a Manifestation of Ovarian Dysfunction, *J. Obst. & Gynaec. Brit. Emp.* 41: 684, 1934.
38. Jones, H. O., and Brewer, J. I.: A Study of the Ovaries and Endometrium of Patients With Fundal Carcinomas, *Am. J. Obst. & Gynec.* 42: 207, 1941.
39. Kurzrok, R.: The Estimation of Estrin and the Follicle Stimulating Hormone in the Urine as an Index of Therapy in Menstrual Dysfunction, *Endocrinology* 16: 361, 1932.
40. Lacassagne, A.: Modifications progressives de l'utérus de la souris sous l'action prolongée de l'oestrone, *Compt. rend. Soc. de biol.* 120: 1156, 1935.
41. Lacassagne, A.: Tumeurs malignes, apparues au cours d'un traitement hormonal combiné, chez des souris appartenant à des lignées refractaires au cancer spontané, *Compt. rend. Soc. de biol.* 121: 607, 1936.
42. Lipschütz, A.: Hyperplasie expérimentale de l'endométrie avec prolifération atypique de l'épithèle utérin après des interventions ovariennes, *Gynéc. et obst.* 36: 408, 1937.
43. Lipschütz, A.: Croissance atypique des glandes du corps utérin, épidermisation de la muqueuse cervicale, troubles de l'équilibre entre ovaire et préhypophyse après des interventions ovariennes, *Gynéc. et obst.* 36: 481, 1937.
44. Lipschütz, A., and Iglesias, R.: Multiples tumeurs utérines et extragénitales provoquées par le benzoate d'oestradiol, *Compt. rend. Soc. de biol.* 129: 519, 1938.
45. Lipschütz, A., Rodríguez, F., and Vargas, L., Jr.: Continuous and Discontinuous Treatment With Estrogens in Experimental Tumorigenesis, *Endocrinology* 28: 664, 1941.
46. Lipschütz, A., and Vargas, L., Jr.: Prevention of Experimental Uterine and Extrauterine Fibroids by Testosterone and Progesterone, *Endocrinology* 28: 669, 1941.
47. Lipschütz, A., Vargas, L., Jr., and Iglesias, R.: Sur la structure microscopique des tumeurs utérines et abdominales dues à l'action du benzoate d'oestradiol, *Compt. rend. Soc. de biol.* 129: 524, 1938.
48. McEuen, C. S.: Metaplasia of Uterine Epithelium Produced in Rats By Prolonged Administration of Oestrin, *Am. J. Cancer* 27: 91, 1936.
49. Mack, H.: Die histologische Bewertung von Hyperplasie der Korpusschleimhaut, nachgeprüft an 200 Fällen, *Zentralbl. f. Gynäk.* 53: 2068, 1929.
50. Martzloff, K. H.: Carcinoma of the Cervix, vol. 2, chap. 51. In: *Obstetrics and Gynecology (Curtis)*, Philadelphia, 1933, W. B. Saunders Company, p. 833.
51. Meyer, R.: Die Pathologie der Bindegewebsgeschwülste und Mischgeschwülste, v. 6, pt. 1. In: *Handbuch der Gynäkologie (Stoeckel)*, München, 1930, J. F. Bergmann, p. 211.
52. Meyer, R., and Kitai, I.: Bemerkungen über endometrane Adenomyosis uteri in anatomischer Beziehung und insbesondere über die histologische Wirkung der heterotopen Zellwucherung, mit kurzer Bemerkung zur Theorie von Sampson, *Zentralbl. f. Gynäk.* 48: 2449, 1924.



53. Migliavacca, A.: Über die Umwandlung des Uterusepithels in syncytiale Struktur unter hormonalen Einflüssen (Beitrag zur Physiopathologie der weiblichen Geschlechtshormone), *Arch. f. Gynäk.* 159: 172, 1935.
54. Nelson, W. O.: Endometrial and Myometrial Changes, Including Fibromyomatous Nodules, Induced in the Uterus of the Guinea Pig by the Prolonged Administration of Oestrogenic Hormone, *Anat. Rec.* 68: 99, 1937.
55. Nelson, W. O.: Atypical Uterine Growths Produced by Prolonged Administration of Estrogenic Hormones, *Endocrinology* 24: 50, 1939.
56. Novak, E., and Martzloff, K. H.: Hyperplasia of the Endometrium—A Clinical and Pathological Study, *Am. J. Obst. & Gynec.* 8: 385, 1924.
57. Novak, E., and Richardson, E. H., Jr.: Proliferative Changes in the Senile Endometrium, *Am. J. Obst. & Gynec.* 42: 564, 1941.
58. Novak, E., and Yui, E.: Relation of Endometrial Hyperplasia to Adenocarcinoma of the Uterus, *Am. J. Obst. & Gynec.* 32: 674, 1936.
59. Oesterlin, E. J., and Cron, R. S.: The Coexistence of Uterine Myoma and Fundal Carcinoma, *Am. J. Obst. & Gynec.* 29: 176, 1935.
60. Overholser, M. D., and Allen, E.: Ovarian Hormone and Traumatic Stimulation of Monkey's Cervix to a Condition Resembling Early Cancer, *Proc. Soc. Exper. Biol. & Med.* 30: 1322, 1933.
61. Overholser, M. D.: Atypical Growth Induced in Cervical Epithelium of the Monkey by Prolonged Injections of Ovarian Hormone Combined with Chronic Trauma, *Surg., Gynec. & Obst.* 60: 129, 1935.
62. Payne, F. L.: The Clinical Significance of Endometrial Hyperplasia, *Am. J. Obst. & Gynec.* 34: 762, 1937.
63. Pfeiffer, C. A.: Some Effects of Testes Transplants in Female Mice, *Anat. Rec. (supp.)* 70: 62, 1938.
64. Pierson, Hannah: Experimentelle Erzeugung von Uterusgeschwülsten bei Kaninchen durch Ovarialhormone, *Ztschr. f. Krebsforsch.* 41: 103, 1934.
65. Pineus, G., and Graubard, M.: Estrogen Metabolism in Cancerous and Non-Cancerous Women, *Endocrinology* 26: 427, 1940.
66. Porter, J. E., and Bramhall, T. C.: Theca Cell Tumor of Ovary and Endometrial Carcinoma, *Am. J. Obst. & Gynec.* 42: 912, 1941.
67. Russell, P. M. G.: A Granulosa-Cell Tumour of the Ovary With Remarkable Hyperplasia of the Uterus, *J. Obst. & Gynaec. Brit. Emp.* 47: 669, 1940.
68. Schiller, W.: Über Frühstadien des Portiocarcinoms und ihre Diagnose, *Arch. f. Gynäk.* 133: 211, 1928.
69. Schmidt, I. G.: Changes in the Genital Tracts of Guinea Pigs Associated With Cystic and "Interstitial Gland" Ovaries, *Anat. Rec. (supp.)* 70: 69, 1938.
70. Schröder, R.: Anatomische Studien zur normalen und pathologischen Physiologie des Menstruationszyklus, *Arch. f. Gynäk.* 104: 27, 1915.
71. Schröder, R.: Granulosazelltumor des Ovars mit glandulärzystischer Hyperplasie des Endometriums und beginnendem Karzinom auf diesem Boden, *Monatschr. f. Geburtsh. u. Gynäk.* 58: 294, 1922.
72. Seegar, G. E.: The Histologic Effect of Progesterone on Hyperplastic Endometria, *Am. J. Obst. & Gynec.* 39: 469, 1940.
73. Selye, H., Thomson, D. L., and Collip, J. B.: Metaplasia of Uterine Epithelium Produced by Chronic Oestrin Administration, *Nature, London* 135: 65, 1935.
74. Siebek, H.: Ergebnisse von Mengenbestimmungen des Sexualhormons. I. Mitteilung. Sexualhormon im Blut, *Zentralbl. f. Gynäk.* 53: 2450, 1929.
75. Stohr, Grete: Granulosa Cell Tumor of the Ovary and Coincident Carcinoma of the Uterus, *Am. J. Obst. & Gynec.* 43: 586, 1942.
76. Taylor, H. C., Jr.: The Coincidence of Primary Breast and Uterine Cancer, *Am. J. Cancer* 15: 277, 1931.
77. Taylor, H. C., Jr.: Endometrial Hyperplasia and Carcinoma of the Body of the Uterus, *Am. J. Obst. & Gynec.* 23: 309, 1932.
78. Taylor, H. C., Jr.: The Pathology of the Ovarian Hormone, *Am. J. Obst. & Gynec.* 36: 332, 1938.
79. Taylor, H. C., Jr., and Greeley, A. V.: Factors Influencing the End-Results in Carcinoma of the Ovary, *Surg., Gynec. & Obst.* 74: 928, 1942.
80. Taylor, H. C., Jr., and Millen, R.: The Causes of Vaginal Bleeding and the Histology of the Endometrium After the Menopause, *Am. J. Obst. & Gynec.* 36: 22, 1938.
81. Tietze, K.: Granulosazelltumor und heterotope Tiefenwucherung der Uterusschleimhaut, *Ztschr. f. Geburtsh. u. Gynäk.* 91: 111, 1927.
82. Witherspoon, J. T.: The Interrelationship Between Ovarian Follicle Cysts, Hyperplasia of the Endometrium and Fibromyomata; a Possible Etiology of Uterine Fibroids, *Surg., Gynec. & Obst.* 56: 1026, 1933.

- 83. Zondek, B.: *Die Hormone des Ovariums und des Hypophysenvorderlappens*, Berlin, 1931, Julius Springer.
- 84. Zondek, B.: Primäre polyhormonale Amenorrhoe mit glandulär-cystisch-hyperplastischer Schleimhaut, *Acta obst. et gynec. Scandinav.* 13: 309, 1934.
- 85. Zondek, B.: The Effect of Prolonged Application of Large Doses of Follicular Hormone on the Uterus of Rabbits, *J. Exper. Med.* 63: 789, 1936.
- 86. Zondek, B.: The Effect of Long-Continued Large Doses of Follicle Hormone Upon the Uterus of the Rat, *Am. J. Obst. & Gynec.* 33: 979, 1937.
- 87. Zondek, B.: The Effect of Prolonged Administration of Estrogen on the Uterus and the Anterior Pituitary of Human Beings, *J. A. M. A.* 114: 1850, 1940.
- 88. Zuckerman, S.: Effects of Prolonged Oestrin-Stimulation on the Cervix Uteri, *Lancet* 1: 435, 1937.
- 89. Zuckerman, S., and Morse, C. H.: The Experimental Production of Excessive Endometrial Hyperplasia, *Surg., Gynec. & Obst.* 61: 15, 1935.

53. Migliavacca, A.: Über die Umwandlung des Uterusepithels in syncytiale Struktur-unter hormonalen Einflüssen (Beitrag zur Physiopathologie der weiblichen Geschlechtshormone), *Arch. f. Gynäk.* 159: 172, 1935.
54. Nelson, W. O.: Endometrial and Myometrial Changes, Including Fibromyomatous Nodules, Induced in the Uterus of the Guinea Pig by the Prolonged Administration of Oestrogenic Hormone, *Anat. Rec.* 68: 99, 1937.
55. Nelson, W. O.: Atypical Uterine Growths Produced by Prolonged Administration of Estrogenic Hormones, *Endocrinology* 24: 50, 1939.
56. Novak, E., and Martzloff, K. H.: Hyperplasia of the Endometrium—A Clinical and Pathological Study, *Am. J. Obst. & Gynec.* 8: 385, 1924.
57. Novak, E., and Richardson, E. H., Jr.: Proliferative Changes in the Senile Endometrium, *Am. J. Obst. & Gynec.* 42: 564, 1941.
58. Novak, E., and Yui, E.: Relation of Endometrial Hyperplasia to Adenocarcinoma of the Uterus, *Am. J. Obst. & Gynec.* 32: 674, 1936.
59. Oesterlin, E. J., and Cron, R. S.: The Coexistence of Uterine Myoma and Fundal Carcinoma, *Am. J. Obst. & Gynec.* 29: 176, 1935.
60. Overholser, M. D., and Allen, E.: Ovarian Hormone and Traumatic Stimulation of Monkey's Cervix to a Condition Resembling Early Cancer, *Proc. Soc. Exper. Biol. & Med.* 30: 1322, 1933.
61. Overholser, M. D.: Atypical Growth Induced in Cervical Epithelium of the Monkey by Prolonged Injections of Ovarian Hormone Combined with Chronic Trauma, *Surg., Gynec. & Obst.* 60: 129, 1935.
62. Payne, F. L.: The Clinical Significance of Endometrial Hyperplasia, *Am. J. Obst. & Gynec.* 34: 762, 1937.
63. Pfeiffer, C. A.: Some Effects of Testes Transplants in Female Mice, *Anat. Rec. (supp.)* 70: 62, 1938.
64. Pierson, Hannah: Experimentelle Erzeugung von Uterusgeschwülsten bei Kaninchen durch Ovarialhormone, *Ztschr. f. Krebsforsch.* 41: 103, 1934.
65. Pincus, G., and Graubard, M.: Estrogen Metabolism in Cancerous and Non-Cancerous Women, *Endocrinology* 26: 427, 1940.
66. Porter, J. E., and Bramhall, T. C.: Theca Cell Tumor of Ovary and Endometrial Carcinoma, *Am. J. Obst. & Gynec.* 42: 912, 1941.
67. Russell, P. M. G.: A Granulosa-Cell Tumour of the Ovary With Remarkable Hyperplasia of the Uterus, *J. Obst. & Gynaec. Brit. Emp.* 47: 669, 1940.
68. Schiller, W.: Über Frühstadien des Portiocarcinoms und ihre Diagnose, *Arch. f. Gynäk.* 133: 211, 1928.
69. Schmidt, I. G.: Changes in the Genital Tracts of Guinea Pigs Associated With Cystic and "Interstitial Gland" Ovaries, *Anat. Rec. (supp.)* 70: 69, 1938.
70. Schröder, R.: Anatomische Studien zur normalen und pathologischen Physiologie des Menstruationszyklus, *Arch. f. Gynäk.* 104: 27, 1915.
71. Schröder, R.: Granulosazelltumor des Ovars mit glandulärzystischer Hyperplasie des Endometriums und beginnendem Karzinom auf diesem Boden, *Monatsschr. f. Geburtsh. u. Gynäk.* 58: 294, 1922.
72. Seegar, G. E.: The Histologic Effect of Progesterone on Hyperplastic Endometria, *Am. J. Obst. & Gynec.* 39: 469, 1940.
73. Selye, H., Thomson, D. L., and Collip, J. B.: Metaplasia of Uterine Epithelium Produced by Chronic Oestrin Administration, *Nature, London* 135: 65, 1935.
74. Siebke, H.: Ergebnisse von Mengenbestimmungen des Sexualhormons. I. Mitteilung. Sexualhormon im Blut, *Zentralbl. f. Gynäk.* 53: 2450, 1929.
75. Stohr, Grete: Granulosa Cell Tumor of the Ovary and Coincident Carcinoma of the Uterus, *Am. J. Obst. & Gynec.* 43: 586, 1942.
76. Taylor, H. C., Jr.: The Coincidence of Primary Breast and Uterine Cancer, *Am. J. Cancer* 15: 277, 1931.
77. Taylor, H. C., Jr.: Endometrial Hyperplasia and Carcinoma of the Body of the Uterus, *Am. J. Obst. & Gynec.* 23: 309, 1932.
78. Taylor, H. C., Jr.: The Pathology of the Ovarian Hormone, *Am. J. Obst. & Gynec.* 36: 332, 1938.
79. Taylor, H. C., Jr., and Greeley, A. V.: Factors Influencing the End-Results in Carcinoma of the Ovary, *Surg., Gynec. & Obst.* 74: 928, 1942.
80. Taylor, H. C., Jr., and Millen, R.: The Causes of Vaginal Bleeding and the Histology of the Endometrium After the Menopause, *Am. J. Obst. & Gynec.* 36: 22, 1938.
81. Tietze, K.: Granulosazelltumor und heterotope Tiefenwucherung der Uterusschleimhaut, *Ztschr. f. Geburtsh. u. Gynäk.* 91: 111, 1927.
82. Witherspoon, J. T.: The Interrelationship Between Ovarian Follicle Cysts, Hyperplasia of the Endometrium and Fibromyomata; a Possible Etiology of Uterine Fibroids, *Surg., Gynec. & Obst.* 56: 1026, 1933.

internal secretion which have to do with mammary function will be described briefly.

### Hormones of the Gonads.—

#### 1. *Ovarian Hormones:*<sup>2, 3</sup>

*Estrogens (The Follicular Hormones).*—It is now generally accepted that the estrogens are capable of developing the duct systems in the breasts of man and animals. In some species acinar development and occasionally secretion may result from this stimulus only. In animals such as the mouse and rat, ductal change alone is noted, whereas in guinea pigs and the primates such as the monkey, lobule aveolar growth occurs as well. In the human subject, estrogens have produced development of the breasts of both sexes and in individuals of all ages.<sup>4, 5</sup> Evidence from several sources suggests an effect on the periductal connective tissue. The variability in effects may not be due to species differences alone, but may depend also upon the dosage level<sup>6</sup> and the structure of the estrogen used.<sup>7-9</sup> Amounts used above a certain level may fail to show additional physiologic change or hyperplasia<sup>10</sup> or may actually produce stunting of the duct systems.<sup>7, 11</sup>

*Progestin (The Corpus Luteum Hormone).*—Since estrogens were incapable of developing the breast beyond the duct system in most species, investigators naturally turned to the corpus luteum. In those instances in which no effect was obtained from progestin alone, simultaneous administration of estrogens induced alveolar and lobular growth.<sup>12</sup> There is no question of the effect of progestin in pregnancy.

#### II. *Testicular Hormones:*

Testosterone and several other androgens are also capable of stimulating the mammary glands in certain species. Ductal development in the rat has been observed by some investigators,<sup>13</sup> while others have noted lobular growth as well.<sup>9, 11, 14</sup> Secretion in the breast of the rat<sup>15</sup> and the monkey<sup>16</sup> has also followed the administration of testosterone and related compounds. Mammary enlargement in eunuchs treated with testosterone is not uncommon.<sup>17</sup> The evidence concerning these actions is not as clear cut as that of the estrogenic effect.

*Hormones of the Adrenals.*—It is fairly certain that the adrenals are concerned in the genesis and metabolism of the sex hormones. Estrogens and androgens have been isolated from the gland in addition to the known cortical hormones. One of the latter group, desoxycorticosterone has been reported to stimulate mammary growth.<sup>9</sup> The adrenals may also be concerned in lactation, but it is possible that this is more closely related to the effects of carbohydrate, water, and salt metabolism rather than to a specific action.

*Hormones of the Pituitary Gland.*—In recent years evidence has accumulated that the hypophysis is also necessary for mammary growth. Two types of hormones have been described.

### I. *Mammogenic Hormones*:<sup>3, 18</sup>

Mammary involution occurs rather promptly after hypophysectomy. It has been reported that the changes usually produced in the breast of animals by estrogens and androgens are not found when the hypophysis is previously removed. Although there have been reports to the contrary, these findings suggested the possibility of a hormone elaborated by the hypophysis. Evidence suggests the existence of such a mammogenic hormone. Turner and his associates postulate that two such hormones may exist. One they term Mammogen I, which they believe responsible for ductal development, and the other Mammogen II, which may cause lobule-alveolar growth.<sup>19</sup> They further believe the former hormone is stimulated by estrogens and androgens and the latter by progesterone and estrogens. Whether these hormones act directly upon the breast or are necessary for the action of the other hormones is not settled.

### II. *Lactogenic Hormone*:<sup>3, 18</sup>

The production of lactation under certain conditions by anterior pituitary extracts led to investigations which resulted in the isolation of a specific lactogenic hormone from the hypophysis—prolactin.<sup>20, 21</sup> Lactation could not be induced in an undeveloped breast, but it was demonstrated subsequently that suitable stimulation by the ovarian hormones was also necessary. Prolactin has recently been highly purified and it has been suggested that this hormone, rather than the mam-mogens, may be a more important factor in mammary development.<sup>22</sup>

These facts emphasize the pituitary-gonadal relationship. They indicate that normally a balance exists between the hormones of these glands; an alteration in this balance may give rise to atypical changes in the organs upon which the hormones act.

#### EVIDENCE FOR A NERVOUS CONTROL OF THE BREAST

Evidence exists that the nervous system is involved in some fashion in the physiologic responses of the breast. Suckling in the virgin rat has resulted in mammary development, lactation, and inhibition of the estrous cycle.<sup>23</sup> This presumably works reflexly by way of the hypophysis. In women suckling certainly plays an important role in the maintenance of lactation. Moreover, there are numerous instances cited of lactation and breast changes in children, the virgin female, and even in the male after stimulation of the nipple alone.<sup>24</sup> Many lesions of the breast are associated with disease in the pelvis, which may affect the breast not only by disturbances of ovarian function, but by way of the pelvic sympathetic nerves.<sup>25</sup> It must be inferred, therefore, that the nervous system is important in the maintenance of mammary function, but probably in an indirect manner, since the elaboration of hormones may be partially initiated by or dependent upon nervous stimuli.

## HISTOLOGIC CHANGES IN THE BREAST DURING THE MENSTRUAL CYCLE

There is evidence that a cyclic change occurs in the breast, which can be correlated with a rise and fall in ovarian activity during the menstrual cycle. One group of writers maintains that in the latter part of the menstrual cycle there is sprouting of the ducts to form acini, which almost completely disappears in the postmenstruum.<sup>26, 27</sup> Others, however, believe this cycle of epithelial proliferation and regression to be exaggerated and are of the opinion that the most striking feature is edema of the connective tissue during the premenstruum.<sup>25, 28</sup> There is also vacuolization of the cells which suggests a secretory phenomenon. Studies of whole sections of the breast have shown that the degree of activity is not similar throughout.<sup>24</sup> This has been attributed to the lack of uniform response to a given stimulus. A similar reaction is known to occur in the endometrium. Since most of the studies were made on small areas of breast tissue, it is apparent that no concrete conception of the changes can be fully determined until whole sections are made from many normal breasts throughout the cycle.

*Conclusions.*—Complete development of the breast is manifested by the presence of certain static structures (ducts, lobules, and acini). Variations of these structures may occur during the menstrual cycle as a result of rhythmical stimulation with the hormones. We have concluded that the breast is prepared each month for pregnancy, since it is subject to the same influence as the uterus. Like the uterus, it has both its proliferative phase induced by estrogens and its secretory phase by progesterin and the anterior pituitary. A process analogous to menstruation then occurs which is represented by some involutional change and absorption of the secretion if pregnancy does not ensue. It is only by accepting these possibilities that one may have a concise and logical explanation for the hormonal and nervous action on the breast, with the resultant changes during catamenia, pregnancy, lactation, and the disease states to be described.

## PHYSIOLOGIC CHANGES IN THE BREAST AT VARIOUS PERIODS OF LIFE

*Birth.*—Activity of the mammary ducts in newborn infants is common. Witches milk also occurs in a fairly high percentage of these babies. This activity probably originates from the hormones of the pregnant mother, since practically complete regression of the infant's breast tissue follows shortly after delivery.

*Puberty.*—After birth the breasts are inactive until the changes leading to puberty appear. In the female, development of the breast usually appears about the tenth year and this is associated with a definite increase in activity of the gonads.<sup>29</sup> At first the changes are confined to the ducts and periductal connective tissue, but even before the menarche there is evidence of acinar and lobule formation. In the

male between the ages of 12 and 17 years there is also a change in the breast.<sup>30</sup> The histologic picture is similar to that observed at the onset of breast growth in the female. These changes usually subside spontaneously in contrast to those in the female, where there is usually continued mammary development once the cyclic activity of the menses is established.

*Adult Cyclic Female.*—In the normal adult female there appears to be a cyclic change in the breast associated with the fluctuations of hormonal secretion during the catamenia. Whether these changes are purely epithelial, vascular, secretory, or combinations of these is a matter of dispute. At any rate there seems to be no doubt that mammary changes do occur during the menstrual cycle and that as stated before they are dependent upon ovarian and pituitary secretions.

*Pregnancy and Lactation.*—The changes which occur during pregnancy and lactation are well recognized and are certainly controlled to a large extent by hormonal secretion. The changes in the breast in the first half of pregnancy are rapid growth of the lobules and epithelial proliferation. In the latter half the acinar epithelium enlarges and secretes, thus causing distention of the acini.<sup>3</sup> During pregnancy the placenta is probably the main source of stimulation, whereas during lactation the pituitary gland is most likely the dominant activator of mammary function.

*Climateric.*—At the menopause when the ovarian stimuli recede to a low ebb, the mammary glands exhibit regressive changes. In some instances, evidence of activity in the breast is apparent years after the cessation of the menses. This may be caused by a continued but lowered secretion of an activating hormone, possibly from the ovary. In other cases, particularly late in life, there may be an almost complete atrophy of the gland.

In summary it may be stated that mammary development, growth, and regressive changes are dependent upon the rise and fall of hormonal stimuli principally from the gonads and the hypophysis. The exact mechanism by which the metamorphosis takes place is still obscure, but present knowledge allows at least a working hypothesis for the understanding of some of the diseases of the breast to be described.

#### PRECOCIOUS DEVELOPMENT (INFANTILE HYPERTROPHY)

Aside from the changes noted at birth there are numerous instances of premature mammary development in children. These are usually associated with demonstrable lesions, although in some cases the etiology is vague.

#### Specific Associated Factors.—

*Lesions of the Third Ventricle:* Tumors, defects, and inflammatory lesions in the region of the third ventricle give rise to true pubertas praecox. The breast changes are merely part of the general picture

of developmental and sexual advance. The most probable explanation for the effect is a stimulation of the hypophysis via the hypothalamus and infundibulum. Ovaries of these patients show marked follicle stimulation and cyst formation and in one instance a true corpus luteum has been reported.<sup>31</sup> The breasts exhibit ductal development but rarely lobule formation. This activity in the ovary probably initiates the secretion of the hormones, which in turn causes growth of the secondary sex organs including the breast. This thesis is confirmed by assays of the urine of these patients, which usually show increased levels of gonadotropic hormone, estrogens, and 17-ketosteroids (androgens).<sup>32</sup>

*Lesions of the Adrenal Cortex:* In general, neoplasms of the adrenal cortex in the female child produce masculinization, but there are cases in which the first signs are feminization.<sup>33</sup> Since the adrenal gland is a probable source of estrogens it is possible to explain the early mammary hypertrophy on this basis especially since excretion studies reveal increased amounts of the hormone.<sup>31</sup> When masculinization and regression of the breasts occur, they are accompanied by significant increases in the androgenic output even though the estrogen levels usually remain elevated. Thus, it is reasonable to assume that this reversal is of androgenic origin and therefore that the androgens are not responsible for the original breast hypertrophy.

*Ovarian Lesions:* Among the associated exciting factors of premature mammary development are lesions such as the granulosa-cell tumor and teratoma of the ovary. These lesions when active are usually associated with generalized feminization, accompanied breast enlargement, uterine bleeding, and cornification of the vaginal epithelium. This syndrome must be distinguished from true pubertas praecox. However, here as in the other states, the breast changes are probably due to estrogens elaborated by the lesions, since the cells involved are those which presumably produce the hormone. Assays of the urine in most instances reveal elevated excretion levels of estrogens, whereas the titres of the other hormones remain normal.<sup>31</sup>

*Idiopathic Breast Development.*—In a few children premature breast development occurs without known cause. Other secondary sex changes are usually normal or only slightly advanced. Histologic examination reveals ductal development, but for the most part assays of the urine for hormones do not reveal any abnormalities.

*Hormonal Induced Infantile Hypertrophy.*—It has been the experience of many that administration of estrogenic hormone to the female child for gonorrheal vaginitis frequently results in mammary growth. There is no question that these changes are due to the hormone since regression occurs rather rapidly after cessation of treatment.

*Conclusions.*—The available evidence suggests that premature mammary development is due in large part to the effect of the estrogenic hormone. It is probable, particularly in lesions of the third ven-



tricle, that the pituitary hormones are also a factor. Histologically the changes are confined for the most part to the duct system and periductal connective tissue. Thus, they correspond to the state produced by a known stimulus and in this sense represent a physiologic response to premature or excess secretion of the hormones. Removal of such a stimulus is followed by a rapid regression to the normal state.

#### HYPERTROPHY OF THE BREAST

*Asymmetrical Prepubertal Hypertrophy.*—At about the age of 10, when normal breast development usually commences, there may be a rapid growth of one breast which is out of proportion to that of the other breast. This is commonly referred to as early ripening and is not true hypertrophy. Eventually the more slowly developing breast usually attains the size of the larger breast and at the time of puberty both are of almost equal size and within normal limits. Since in most females the breasts are not identical in size, this seems to represent an exaggeration of a normal phenomenon. Histologically the changes are no different than those in the normal adolescent. Estrogen excretion is usually normal. The early inequality is explained by some investigators as an increased sensitivity of the involved organ to a normal physiologic stimulus.<sup>34</sup>

*Pubertal and Postpubertal Hypertrophy.*—Pubertal and postpubertal hypertrophy abnormalities may be classed as true hypertrophy. The process is either unilateral or bilateral and is easily distinguished from early ripening by the size of the breast. It may manifest itself at puberty although similar changes are associated with pregnancy and lactation. Histologically there is an increase in ductal growth, but connective tissue increase is more striking. Lobular development is rare especially in the virginal type. Estrogen assays are usually normal, but may show elevated levels of the hormone. Again, as in early ripening, the changes may be due to an excessive stimulation or to increased sensitivity of the breast.

#### FIBROADENOMA OF THE BREAST

Observations suggest that these tumors may be of hormonal origin. It is possible that they may arise as a result of abnormal or excessive stimulation, since they usually occur when the metabolism and secretion of the sex hormones are at their height and may, in addition, be abnormal.

*Clinical Aspects.*—The lesions seldom develop before puberty or after the menopause, except possibly in the presence of a granulosa-cell tumor or similar abnormality of the ovary. They are seen most frequently in the second and third decade. It has been suggested that fibroadenomas occur most frequently in women of a definite constitutional type, that is, nulliparous females with a relative underdevelopment of the pelvic organs and breasts.<sup>35</sup> The menstrual cycles of

patients with fibroadenomas of the breast are seldom abnormal, but some give a history of a period of atypical cycles following the menarche. Endometrial biopsies on such patients do not reveal any gross abnormality. Since these lesions arise most frequently prior to pregnancy, the reproductive history is not of significance. The incidence of pelvic disease in patients with fibroadenoma is relatively small when compared with that in other types of benign breast disease. Abnormalities present in the earlier years are usually underdevelopment of the pelvic organs or are congenital in origin.

*Experimental Studies.*—Studies on the occurrence, alteration, and production of these lesions in the experimental animal and the human being are of interest with regard to the possibilities of hormones as etiologic agents. It has been reported that estrogen pellets or estrogens with prolonged activity produce a high percentage of true fibroadenomas in a strain of rats which ordinarily have a low spontaneous incidence of the disease.<sup>36</sup> Although others have been unable to confirm these findings, neither the method of estrogen administration nor the strain of rats was identical.<sup>37</sup> In our clinics, patients have been given estrogens over a long period in the presence of and following the removal of fibroadenomas. No new tumors have been observed which could be attributed to the hormone. On the other hand, it is not uncommon for new lesions to arise spontaneously when others are already present. Regarding the activity of fibroadenomas under hormonal influences, there can be little doubt. Changes have been observed in the size and histology of the tumors during the menstrual cycle,<sup>37</sup> pregnancy, and lactation.<sup>38, 39</sup> Androgens decrease the glandular elements in both the spontaneous and transplanted fibroadenomas of rats and may convert them to fibromas.<sup>40, 41</sup> Studies in this laboratory reveal that androgens may produce atrophic changes in the breast epithelium and may actually cause disappearance of the terminal tubules of the mammary gland of the mouse. In short, therefore, fibroadenomas, at least in the experimental animal, unlike carcinomas of the breast are subject to the same changes as normal breast tissue. It is difficult to see why a circulating hormone should not affect the breast uniformly. Yet there is evidence that the response of the breast is not uniform to such a stimulus. Since the histologic characteristics of the fibroadenoma are similar to those seen in the normal breast, it has therefore been suggested that the lesions are not actual tumors but because of a localized sensitivity represent a specific response to normal stimuli.<sup>6, 34</sup>

*Excretion Studies.*—Studies of the urinary excretion of estrogens have been carried out in eight patients with the disease.<sup>42</sup> Some of the patients developed more tumors during the period of observation. Assays were continued throughout a minimum of one menstrual cycle. In the majority of cases the monthly curve of excretion resembled those

of normal controls in the same age group although a few had atypical curves. The latter may represent an abnormal excretion, but there is no direct evidence that they are characteristic for the disease. The process is slow and since all patients were studied after the onset of the disease it is possible that abnormalities may have been present earlier. The findings do not prove that estrogens are not involved since, as stated before, the tumors may arise as a result of a localized response to normal stimuli. Furthermore, excretion rates as will be pointed out later, must be interpreted with caution, since they represent only one index of activity.

*Conclusions.*—There is a suggestion that estrogens are involved in the initiation of fibroadenoma of the breast. The lesions are usually slow growing and, although not noticed, may arise in the early years after the menarche when atypical menstrual activity is not uncommon. They resemble the changes seen in early ripening and hypertrophy and may represent a more localized response to a normal stimulus. There is no direct proof, however, that the hormones are the exciting agents, in spite of histologic alteration during various physiologic states or after hormonal administration. The possibility of a definite constitutional type must be considered. One is forced to conclude, therefore, that factors other than hormones may be operating as well.

#### CHRONIC MASTITIS, CYSTIC DISEASE, AND PAPILLOMAS

The terms chronic mastitis or chronic cystic mastitis have been used to denote a variety of benign lesions without obvious tumor formation. It is now recognized that some of the lesions included under such diagnoses can be distinguished as definite entities. For an understanding of possible causative factors it seems preferable to establish a working classification, based on clinical and microscopic observations. No one classification has been found to be satisfactory because of disagreement among pathologists and clinicians. The classification to be offered here is not original, but is an attempt to combine our own observations with those of others. Even though there are obvious discrepancies, it is helpful in differentiating the various manifestations of breast disease and their possible causative factors.

*Adenofibrosis.*—A syndrome for which Taylor<sup>43</sup> has suggested the term adenofibrosis seems to be a distinct entity. Semb<sup>44</sup> has referred to the lesion as fibroadenomatosis. Probably the earliest signs and symptoms are those of premenstrual swelling and pain associated with tenderness of the breast. The relief usually following the onset of the menses is dramatic. This early stage is commonly referred to as mastodynia or mastalgia. The physical signs are usually minimal and, beside slight premenstrual swelling and venous engorgement, may show only a slight thickening in the upper outer quadrant. Histologically there may be only a slight increase in the periacinar connective

tissue, and edema. As the process continues, the symptoms and signs become more prominent. There may be only an accentuation of nodularity in the upper outer quadrant, but usually the process is more diffuse. There is an increase in density of the entire gland, which is well differentiated from the overlying skin, the subcutaneous tissue, and the underlying structures. In the advanced cases, the entire breast resembles a saucer or disc and a definite edge can be palpated. The gland may be finely granular or moderately nodular, and in the premenstruum exhibits marked swelling and venous dilatation. Histologically there is usually a marked increase in the connective tissue stroma with loss of or defective lobule formation. Frequently in addition to the stromal change there is proliferation of the acini, although the epithelium itself may not show activity. Many variations of the process may be seen. In most cases venous engorgement and edema are prominent features, especially in the premenstruum. This may account for the typical cyclic pain. It appears to be the basic process and other features such as epithelial proliferation may be superimposed as a later manifestation.<sup>45</sup> For a detailed and excellent description of the syndrome and its histologic features one is referred to the work of Taylor and Waltman.<sup>45</sup>

*Clinical Aspects:* Adenofibrosis most commonly occurs in the second and third decade of life, and in this respect resembles the fibroadenoma. Regression occurs after the menopause or following castration. A study of the menstrual cycle by most observers reveals that shortened intervals accompanied by a scant flow of short duration is not uncommon.<sup>34, 35</sup> The cyclic character of the pain during the cycle has been described. Endometrial biopsies usually reveal normal patterns. The incidence of sterility is relatively high. In those women who have borne children, the process is sometimes seen after a long period of infertility. Disease of the pelvic organs frequently accompanies the breast change. Taylor is of the opinion that so-called pelvic congestion or chronic parametritis is a salient associated lesion.<sup>25</sup> Permanent changes may thus result from such chronic congestion. He further believes that these two conditions may be produced by a similar process, which is at least partially dependent upon disturbances of the vascular and nervous systems. Such disturbances may possibly arise from, or may lead to, endocrine dysfunction.

*Experimental Studies:* Many attempts have been made to reproduce these lesions in experimental animals. Geschickter<sup>46</sup> injected rats with a daily maximal physiologic dose of estrone and noted changes resembling adenofibrosis. This was also obtained by combining injections of progesterone or testosterone with larger doses of estrone. Taylor and Waltman<sup>45</sup> were unable to produce these lesions in mice. These differences may possibly be reconciled by a consideration of the type and dosage of hormone used and by difference in the strain or

species of experimental animal. The production of edema may be due to the hormones of the ovary since they have been shown to cause retention of fluid.<sup>47</sup> Increased vascularity may be produced by estrogens, although nervous stimuli may be responsible either by a direct action or indirectly through activation of hormonal secretion.

*Excretion Studies:* Taylor<sup>25, 43</sup> could find no gross abnormality either in the total output or the configuration of the monthly curve of estrogen excretion. Bucher and Geschickter<sup>48</sup> made similar observations but stressed the total output. Nathanson<sup>49</sup> studied the cycles of excretion but did not attempt to estimate the total output since the configuration of the curve was considered more significant. Some of the patients exhibited atypical curves although such abnormalities were not constant from month to month. An analysis of several of the curves presented by Taylor and Bucher and Geschickter also suggests a similar anomaly of excretion, which is not usually found in a woman with a normal cycle. When one considers the configuration of the excretion curves, these three studies seem to be in essential agreement with regard to estrogen excretion.

A study of the possible role of the corpus luteum hormone has also been made. Nathanson noted a lowered excretion of pregnandiol in only a few of the cases studied while Bucher and Geschickter found similar changes in all of their patients. Assays of the gonadotropic hormone by Taylor and by Nathanson revealed no gross alterations.

*Conclusions:* Adenofibrosis of the breast represents a distinct entity. The secretions of the ovary seem to be a prerequisite for the production of the syndromes although they may not be the exciting factors. Nervous stimuli, vascular reactions, and the mechanism of hormonal secretion are closely interwoven, so that all three factors may be involved in the process, particularly regarding the edema and congestion. Excretion studies are slightly suggestive of a hormonal imbalance. The possible role of unopposed or atypical stimulation by the hormones also remains to be clarified. Slight abnormalities of the menstrual cycle and associated pelvic disease suggest a hormonal etiology. It can be concluded as in the case of fibroadenoma that the hormones are possibly involved but that other factors are also necessary for the production of the syndrome.

**Nonpuerperal Secretion.**—The salient feature of this type of breast disease is discharge from the nipple which may be accentuated before the menses. The process is sometimes associated with swelling and cyclic or acyclic pain. The discharge may abate at the menses, but usually persists throughout the cycle. It may be serous or resemble colostrum and show varying degrees of viscosity. It is to be distinguished from the serosanguineous or sanguineous discharge so frequently associated with duct papillomas, marked epithelial hyperplasias, and carcinoma. Examination usually reveals dilatation of the

ducts, especially near the areola, and slight nodularity elsewhere in the breast. The nipples are frequently crusted and the mammary tissue itself is ill-defined. If secretion is not obvious, removal of the crust with gentle pressure on the breast usually results in the escape of fluid from the nipple. On gross and microscopic examination the ducts are dilated and contain secretion, desquamated cells, and debris. Frequently, cheesy inspissated material is seen. Hyperplasia of the duct and acinar epithelium may be superimposed.

*Clinical Aspects:* These lesions occur most frequently during the third and fourth decades. Many cases appear at onset of the menopause. Remission of symptoms and signs is of frequent occurrence after castration or when the menopause is complete. The menstrual cycles may be normal, but prolongation of the interval is common. In contrast to the findings in adenofibrosis the endometrium is frequently atypical. Absence of the secretory phase is most common, although hyperplasia is relatively rare.<sup>50</sup> In contrast to adenofibrosis, many women with this disease have borne children. Lactation may be normal but faulty lactation or premature weaning frequently precedes the onset of the disease. Pelvic disease is fairly common in this group. Ovarian cysts predominate over other abnormalities.

*Experimental Studies:* Prolonged injection of estrogens in mice results in changes similar to those described in the human being.<sup>45</sup> The rat also shows a similar reaction particularly when estrogen administration is followed by prolactin.<sup>6, 11</sup>

*Excretion Studies:* The excretion of estrogens throughout the menstrual cycle is definitely atypical in a high percentage of cases. It was found that the peaks ordinarily seen at the time of ovulation and at the height of corpus luteum function were frequently absent.<sup>51</sup> Moreover, the daily excretion was somewhat lower than that observed in normal subjects. Taylor<sup>43</sup> also came to the same conclusion from an interpretation of the configuration of the curve and the total monthly output. Pregnandiol excretion in these patients is usually lower than normal.<sup>51</sup> There is no consistent abnormality in the excretion of the gonadotropic hormone, although there is a suggestion of an excessive output particularly in the premenopausal group.

*Conclusions:* Nonpuerperal mammary secretion seems to be due to endocrine dysfunction. It is akin to lactation and is frequently allied with abnormalities of the process. It is probably due to an ovarian dysfunction, in which the normal cyclic secretion of estrogens is absent. Deficiency of the corpus luteum as evidenced by lowered pregnandiol excretion and atypical endometrial biopsies is also of importance. Such a state is suggestive of an anovular cycle, a state which often occurs in the premenopausal period when the breast lesions frequently make their appearance. The process could, therefore, be caused by continuous estrogen stimulation, which is unopposed or not supple-

mented by the corpus luteum hormone and, thus, may be analogous to the production of similar lesions in mice. As a part of the dysfunction there may be an alteration of the pituitary secretion, so that this, too, may be a factor in the production of the syndromes.

**Combined and Miscellaneous Types.**—Unfortunately, many of the lesions seen by the clinician are not as clear cut as those described. There may be combinations of adenofibrosis and nonpuerperal secretion. Others may show, in addition, cyst and papilloma formation. The latter may be superimposed on the two basic lesions described.<sup>45</sup> Such a phenomenon may occur when the less complicated lesions are of long standing and are subjected to continuous or new stimulation. This group of mixed lesions leads to the greatest confusion in diagnosis and interpretation of causative factors. At present because of an incomplete understanding of these types, it is difficult to evaluate possible exciting factors. Lesions resembling the various types have been produced in animals by various hormones, particularly the estrogens. At any rate one may be safe in assuming that factors concerned in the production of the more clear-cut lesions may also be responsible in the production of this heterogenous group.

### **Cystic Disease of the Breast.**—

*Clinical Aspects:* True cystic disease of the breast may manifest itself in a variety of forms. It usually occurs in women in the latter part of active sexual life and is especially common about the time of the menopause. Unlike adenofibrosis or nonpuerperal secretion, regressions following the menopause are infrequent. Diseases of the breast such as those described may precede cystic disease. The menstrual cycles are usually normal. Cyclic swelling and subjective and objective symptoms other than the presence of lumpiness of the breast are conspicuously absent. The disease occurs most frequently in the childless woman, and the incidence of coexistent pelvic disease is not unusual. The physical findings are well recognized, but the process must be carefully distinguished from the lesions previously described.

Three well-defined types are seen :

1. Cysts without epithelial hyperplasia
2. Multiple cysts with epithelial hyperplasia (Reclus' disease)
3. Multiple cysts with marked epithelial hyperplasia and papillomatous change (Schimmelbusch's disease, adenosis).

The solitary cyst is primarily of duct origin, while the lesions with multiple cysts may show the greatest change in the acini.

*Experimental Studies:* The various manifestations of cystic disease in the woman can be duplicated by the administration of estrogens alone<sup>52, 53</sup> or in combination with prolactin<sup>6, 11</sup> to the experimental animal. Some believe estrogens to be the causative agent in the human being and Geschickter has reported the development of cystic disease following

such stimulation in the woman.<sup>34</sup> In our experience even when the hormone is given to patients with the disease, no changes have appeared which could be ascribed to hormonal administration.

*Excretion Studies:* In this laboratory, no constant pattern of excretion of estrogens was found in patients with cystic disease. As in the other types of benign breast disease, atypical cycles of excretion were encountered, but the deviation from normal was not sufficiently great to warrant an assumption that they were significant. Pregnandiol excretion was also variable. Bucher and Geschiekter<sup>48</sup> found extremely low values of pregnandiol in two cases and equivocal curves of estrogen excretion.

*Conclusions:* Cystic disease in the human being can be simulated by the administration of hormones to animals. Other evidence, also, suggests the internal secretions as participating agents. However, as in most other processes ordinarily included under this heading, the data are still far from conclusive regarding the hormones as the primary cause.

#### BENIGN BREAST DISEASE IN THE MALE

As in the female, benign disease in the male breast is erroneously designated as mastitis. Some refer to most types as gynecomastia, but this should be reserved for a special group.

*Adolescent or Puberty Mastitis.*—In the male, this is akin to that seen normally at the onset of the breast development in the female. It usually appears between the twelfth and seventeenth years. It is characterized by the presence of a well-defined, freely movable, discoid mass beneath and closely associated with the areola. The mass may vary in size from less than 1 to 5 cm., but as a rule is 2 to 3 cm. The nipple and areola may also be increased in size. The process is usually unilateral at the onset, but may affect both breasts, simultaneously or successively. It occurs more commonly than is generally recognized. Jung and Shaf-ton in approximately 1,000 examinations found that it was an integral part of the process of puberty.<sup>30</sup> It is not seen more often because of the frequently transient character of the process, which may arise and regress within even a month. Histologic examination reveals lengthening and hypertrophy of the ducts, with an increase in periductal connective tissue. Lobule formation is usually absent. In a small percentage of cases this lesion persists and may then be correctly called gynecomastia.

*Gynecomastia.*—In the abnormality of gynecomastia, the contour and elements of the breast approach that of the normal woman. As stated previously, it may represent a persistence of the adolescent type or may arise spontaneously in the adult in the presence of associated diseases. It may be unilateral or bilateral. Histologically, in addition to the changes described, there may be hyperplasia of the duct epithelium, dilatation of the ducts, and occasional secretion. The presence of acini



and lobules is rare. The main differences from the other types of benign breast disease in the male are the persistence and the physical characteristics.

*Recurrent Mastitis.* After the age of 45 years, but particularly after 60, changes resembling those seen at puberty are frequently encountered. Some, of course, may occur earlier. The disease behaves in a fashion similar to that seen in the youth, but spontaneous regression is not as common.

*Possible Etiologic Factors.* In the large majority of cases, there are no obvious associated abnormalities. Adolescent and recurrent mastitis, as noted, occur at the extremes of active sexual life. It is possible, therefore, that at these periods there is a temporary hormonal imbalance. However, both mastitis and gynecomastia may occur in association with other diseases and in these instances possible etiologic factors are apparent. These may be described as follows:

1. *Atrophy of the Testicle Following Orchitis or Injury.* The spermatogenic tubules are most commonly atrophied and the atrophy thus accompanied by a relative or actual increase in the interstitial cells. Since the latter are supposedly the site of origin of androgens, it is possible that they are responsible for the change in the breast.

2. *Neoplasms of the Testes.* Gynecomastia is sometimes associated with tumors of the testes, particularly the chorioepithelioma. Gilbert<sup>64</sup> is of the opinion that the breast lesions are of two types: (1) a "physiologic" type resembling the usual mastitis in males and not necessarily related directly to the tumor of the testes; (2) a "choriogonic" type most frequently related to the chorioepithelioma, and resembling the female breast in its histologic characteristics, especially during pregnancy. The pituitary gland in cases with "choriogonic" gynecomastia shows changes which are also seen in pregnancy. In contrast to the physiologic type, these lesions may be caused by the hormones secreted by the tumor itself. Several cases of gynecomastia have also been associated with interstitial cell tumors of the testes. The nature of the stimulus is not clear, for although one would expect the androgens to be in excess, one patient<sup>65</sup> had loss of libido suggesting destruction of testicular function and failure of the tumor to secrete a hormone to maintain such a function.

3. *Functioning Tumors of the Adrenal Cortex in the Adult Male.* These may produce feminization in contrast to the usual masculinizing syndrome seen in females and young males.<sup>66, 67</sup> The syndrome is characterized by mammary enlargement, regression of secondary sex characters, and atrophy of the testes. Since estrone as well as androgens have been recovered from the adrenal gland, and because elevated excretion levels of both of these substances are frequently found in patients with adrenal cortical tumors, a hormonal cause seems evi-

dent, especially since removal of the tumor is followed by regression of the breast lesion.

4. Hypophyseal Adenoma.<sup>54</sup> These lesions may give rise to atypical pituitary secretion which may affect the breast directly or indirectly as a result of stimulation of the peripheral endocrine organs.

5. Cirrhosis of the Liver. Breast changes associated with cirrhosis are sometimes encountered.<sup>55</sup> The patients commonly show associated testicular atrophy. It is conceivable that the breast lesions may be caused by faulty metabolism of the hormones as a result of the cirrhosis, since the liver is intimately concerned with such a metabolism. An alternative possibility is a loss of testicular function.

6. A Syndrome Characterized by Aspermatogenesis, Testicular Atrophy, and Gynecomastia Without Known Cause, as reported by Klinefelter and co-workers.<sup>60</sup> The testicular changes resembled those seen after orchitis or injury, and may possibly fall into the same category.

7. Other Conditions. The mechanism involved in the production of mastitis in patients having thyrotoxicosis,<sup>61</sup> leucemia, and other diseases is not clear. It seems, however, that in these diseases there is also a disturbance in the metabolism of the hormones.

8. Hormonal Induction of Mastitis and Gynecomastia. Mastitis of a transient character develops in eunuchs following the injection of testosterone.<sup>17, 62</sup> Such treatment is followed by an increased excretion of estrogens in the urine and suggests, therefore, a metabolism or conversion of the androgens to estrogenic substances.<sup>63-65</sup> This may be characteristic for the eunuch, since such changes after administration to a normal individual are exceedingly rare. As would be expected, the administration of estrogens to the male results in mammary hypertrophy.<sup>66-69</sup> The nipples and areola enlarge and in some cases there is marked epithelial proliferation and acinar formation. Removal of the stimulus allows for relatively rapid regression of the process.

#### *Excretion Studies.—*

*Adolescent Mastitis:* A study of the excretion rates of the sex hormones in adolescent mastitis has revealed that in many instances the process is associated with atypical urinary excretion rates of estrogens and 17-ketosteroids, probably as a result of sexual metamorphosis.<sup>70</sup> From the data, it appeared that the mastitis occurred in the presence of a hormonal imbalance in which the estrogens played the more important part. The syndrome was more closely related to the ratio of the estrogens to the 17-ketosteroids than to individual rates. There was evidence of pituitary hyperactivity in some cases, but the data were not conclusive.

*Senescent Mastitis:* Changes in sex hormone excretion similar to those of the adolescent type are usually found.<sup>71</sup> The estrogens are within normal range, the 17-ketosteroids below normal, and the gonadotropic

titer almost always elevated. It should be pointed out that these levels are similar to those observed in the older male, particularly at the climacteric, so that their significance is open to question.

*Gynecomastia and Mastitis in Association With Known Abnormalities:* Gynecomastia without known cause is accompanied by excretion rates of the hormones much like those of the adolescent and senescent types. Frequently the values are normal, but it should be remembered that the studies in most cases were made after the process became static. When there are associated abnormalities, hormonal excretion is usually atypical. Certain testicular neoplasms, especially the embryonal carcinoma and the chorioepithelioma, give rise to marked elevations of anterior pituitary-like hormone which, as far as can be determined, is similar to that excreted in pregnancy.<sup>52</sup> Moreover, significant elevations of estrogen excretion may be found in patients with associated gynecomastia and chorioepithelioma.<sup>51</sup> Androgen excretion is variable depending upon the extent of testicular destruction. In one case of interstitial cell tumor an increase of the gonadotropin titer was found.<sup>55</sup> Cases of feminization due to adrenal cortical carcinoma show estrogen levels out of proportion to the androgen excretion rates.<sup>57</sup> The hormonal excretion in patients with hypophyseal adenoma has not been studied, but there is reason to suspect that atypical excretion levels are present. Klinefelter and his associates<sup>60</sup> found increased follicle-stimulating hormone (gonadotropic hormone), normal to lowered 17-ketosteroids, and normal estrogens in their patients with aspermatogenesis. They are of the opinion that the breast lesions are not due to hyperestrinism nor androgens alone, but rather to a combination of androgens and lack of inhibin (a hormone similar to estrogens secreted by the testicular tubules). Glass and associates<sup>69</sup> studied the excretion of estrogens and androgens in males with mastitis and hepatic disease. They found low androgen values and elevated levels of the free estrogens. The testicular atrophy associated with these cases may account for the low androgen levels, and faulty metabolism in the liver might explain the high values of estrogens.

*Conclusion:* Benign breast disease in the male seems to be associated with an endocrine imbalance, either as a result of sexual metamorphosis or of an associated abnormality or tumor. Since the changes normally produced by the various hormones are not identical, clarification may come when a careful correlation is made between the histologic appearance of the breast and a known activating agent. A common denominator may be found in the mammogenic hormones. As stated previously they may be activated either by estrogens or androgens. Hence, similar lesions could be produced by these different hormones. Most of the available data point to the estrogens as an important factor. Changes induced in the breast by the administration of estrogens are seen frequently, but except in the eunuch testosterone seldom produces obvious breast abnormalities. Moreover, testosterone has been

used with success in the treatment of the more transient types of mastitis. These paradoxical findings may possibly be explained by a difference in the metabolism of the hormones as a result of disease or alteration of the endocrine status of the individual.

#### CARCINOMA OF THE BREAST

Numerous observations have been made suggesting a possible relationship between the glands of internal secretion and carcinoma of the breast. These studies, both clinical and experimental, are of importance since they have provided tools and leads by which one may search for a specific cause of the disease.

*Experimental Studies.*<sup>73, 74</sup>—The work of Tyzzer,<sup>75</sup> Slye,<sup>76</sup> and others established the importance of heredity in the development of tumors in mice, but later work suggested that other factors were also involved.<sup>77</sup> Lathrop and Loeb, in 1916, demonstrated that castration caused a marked reduction in the incidence of spontaneous mammary carcinoma in mice with a high susceptibility to the disease. It was later shown that the reduction in rate varied directly with the age of castration, that is, the earlier the ovariectomy, the lower the incidence. Castration also delayed the appearance of tumors when they did arise.<sup>79, 80</sup> However, when female mice of a normally high-tumor strain were spayed immediately after birth the incidence of breast tumors was higher than in mice castrated at maturity.<sup>81</sup> It was suggested that the adrenal glands substituted for the ovaries, since mammary and uterine stimulation was noted and adrenal cortical hyperplasia developed later in life. Murray<sup>82, 83</sup> found that mammary cancer could also be produced in males of highly susceptible strains by the transplantation of ovaries of their sisters, and also noted a lower rate in virgin females. Bagg<sup>84</sup> observed that forced breeding increased the incidence of mammary tumors. Pekete found that the mammary glands of mice of high-tumor strains showed more proliferation during pregnancy in contrast to those of a low-tumor strain during the same period. Moreover, regression of the glands in the high-tumor strain was incomplete after parturition.<sup>85</sup> These experiments suggested the importance of the ovary in the production of the lesions. Attempts to produce breast cancer in the animal by the use of estrogenic substance were not successful until the work of Lacassagne in 1932.<sup>86</sup> By the administration of the hormone, he was able to produce cancer in male mice which never have the disease, although the incidence in the females of the same strain is high. It was not possible, however, to initiate cancer in males belonging to a very low mammary tumor strain.<sup>87</sup> Many others have since confirmed and extended the work.<sup>73, 74</sup> They have reaffirmed the influence of heredity as a necessary factor in oncogenesis, regardless of the other agents involved. Recently, it was shown by Bittner that another factor which was present in the milk of high-tumor strains was also essential.<sup>88, 89</sup>

By suckling newborn females of a low-tumor strain on mothers of a highly susceptible strain, the incidence of tumors could be significantly increased. A reduction in rate was seen when the reverse procedure was carried out. Twombly<sup>90</sup> utilized this technique and was then able to produce breast cancer in the males of low-tumor strains by the administration of estrogens. Thus, it has been demonstrated that factors other than the estrogens alone are necessary for the production of mammary cancer. It has been maintained that the extent of response of breast tissue of nonsusceptible animals to estrogens is limited regardless of the duration of administration or the amount of hormone given. Factors which ordinarily control cell growth may act to prevent further progression of the cells to a malignant state. Defects in the governing mechanism may allow for neoplastic changes, providing the cells are susceptible. The recent report of Geschickter<sup>36</sup> is at variance with this point of view. He has reported a high incidence of mammary cancer induced by prolonged administration of estrogens in rats of a nonsusceptible Wistar strain. Metastases were also described. Noble and collaborators<sup>91</sup> using essentially the same technique in a different strain of rats noted tumors which were extremely hyperplastic, but there was no evidence of invasion of the stroma or rupture of the basement membrane by the cells. The tumors were not considered malignant, even though they were similar to the lesions described by Geschickter, except for the metastases. If the findings of cancer production in species of a non-tumor genetic constitution can be confirmed, the role of the estrogens as etiologic factors may assume greater significance.

Nathanson and Andervont<sup>92</sup> and others,<sup>93, 94</sup> since, have demonstrated that testosterone administered under proper conditions will partially inhibit the appearance of mammary cancer in a highly susceptible strain. This presumably is brought about by an antagonism to the estrogens or by the inhibition of pituitary activity. The hormone, however, has no effect on the tumor once it has developed. Other glands of internal secretion may also be of significance. For example, Cramer and Horning<sup>95</sup> have described a "brown degeneration" in the adrenal which appears to be commoner in the more susceptible strains of mice. Cancer of the breast has also been produced by transplantation of lobes of the anterior hypophysis, but it does not arise in the absence of the ovary.<sup>96</sup> It is now agreed by most observers that at least three factors as suggested by Bittner are necessary for the genesis of breast cancer in the mouse.<sup>99</sup> These are (1) a hereditary influence, (2) the presence of the ovary or its secretions, and (3) the milk factor. All three must be present or cancer does not develop in the experimental animal except possibly in the exceptional case. Moreover, it can be stated at present that the estrogens are not in themselves carcinogenic, but merely provide the substrate upon which an exciting agent may act.

*Clinical Aspects.*—A study of 2,165 cases of cancer of the breast revealed that the peak of age incidence was reached in the group between 46 to 48 years of age.<sup>97</sup> The median age was 52 years; that is, as many cases occur in patients before this age as after it. About a third of the patients are under 45 years, another third from 45 to 55, and the remainder thereafter. Taylor<sup>98</sup> has compared the time of onset of the disease to the time of the menopause and states that about one-third of the cases occur during the period of mature ovarian function, another third appear within five years before or after the menopause, while the remainder develop in women whose ovarian function has ceased for five years or more. These studies, therefore, are in agreement. It must be pointed out, however, that this represents the age incidence seen in hospitals and is not a true cross section of the entire community. When the incidence in the general population is considered, it has been shown that susceptibility to cancer of the breast increases steadily with age.<sup>97</sup>

It is not known definitely whether women who develop cancer of the breast at any period of life have or have had a higher percentage of menstrual disturbances than those who do not. It has been observed, however, that the menstrual pattern changed shortly before the discovery of the disease.<sup>35</sup> The association of breast cancer with lesions in the pelvis is similar to that observed in other types of breast disease. Taylor noted a fairly close association with tumors of the female pelvic organs suggesting that the entire reproductive system may be subject to the same abnormal stimulus.<sup>98</sup>

It is an accepted fact that nulliparous women have a higher incidence of cancer of the breast than those who have borne children.<sup>99, 100</sup> This is extremely interesting in view of the fact that cancer of the cervix is more common in the multiparous female than the virgin. This situation appears to be the reverse of that found in the experimental animal. The question of lactation is, also, of great interest. It is held by some observers that early weaning of the child or faulty lactation for various reasons conduces to the development of breast cancer.<sup>99-101</sup> This is based on the supposition that atypical lactation results in stasis and breakdown products which may cause chronic irritation, and thus may possibly lead to cancer. Experiments in mice relative to this point have shown that blockage of the mammary ducts with resulting milk stagnation was influential in determining the site and time at which tumors appeared in a susceptible strain, but did not in itself cause an increased incidence.<sup>102</sup> Taylor, in a careful study of approximately 350 children of women with breast cancer, found that 72 per cent were nursed for at least six months; of the remainder a very small number were deliberately weaned and the others were not nursed because of an inadequate milk supply.<sup>35</sup> It would be interesting to know if women with cancer of the breast had normal lactation after every pregnancy. Comparison of the data with normal

women may reveal important information. This problem may now be more easily settled because of the present-day practice of early weaning and suppression of lactation. It is too early to evaluate such material. As pointed out by Taylor, further studies of lactation may be significant because there may be evidence of inflammation resulting from stasis of secretion, or there may be an indication of an abnormal physiologic state, which in itself may predispose to cancer of the breast.<sup>95</sup>

Data in relationship to the menopause are also suggestive. Oleh compares the onset of the menopause in normal patients and in those with breast cancer.<sup>103</sup> From his studies, he found that approximately 72 per cent of normal women pass through the menopause at the age of from 40 to 50 years, while 55 per cent of these with cancer are still menstruating at the age of 50. It was concluded that almost five times as many women with cancer of the breast had a delayed menopause as compared to those with a normal climacteric. The average age of the woman in menopause is cited by most observers as 48 years. Since the median age in cancer of the breast is 52 years, one may speculate further on a possible endocrinologic relationship. Inasmuch as disturbed ovarian function is common at the climacteric, it may thus prepare a suitable substrate for the development of the disease. Moreover, tumors which appear later may arise on atypical changes, which originate much earlier. The process described as chronic cystic mastitis may fall into this category. Even though amenorrhea is one of the primary signs of the menopause, the ovary frequently continues to secrete estrogenic hormone in considerable amounts for a relatively long period of time thereafter.<sup>104</sup> In castrate patients and in those many years past the menopause, when all histologic evidence of ovarian activity has disappeared, estrogens are still recovered in the urine. Another probable source of these hormones is the adrenal gland. It is possible, therefore, that stimulation of the breast continues, although it may be entirely different than that in the years when menses are still present.

*Development of Carcinoma on Benign Lesions.*—The significance of a relationship between certain types of chronic cystic mastitis and carcinoma of the breast is a subject of much controversy. Observations in this regard have been based on the coexistence of the two diseases, the development of cancer in previously proved cystic disease, and the study of changes leading to cancer in the experimental animal and the human being. The important literature concerning this problem has recently been reviewed by Lewis and Geschickter,<sup>105</sup> Warren,<sup>106</sup> and Logie.<sup>107</sup> Of the recent writers, Lewis and Geschickter are not agreed that most types of chronic cystic mastitis are precancerous, and the further statistical confirmation of Logie strongly supports the contention of those who postulate a definite causal relationship between the two conditions. The discrepancies may be partly

explained by the criteria set up for the diagnosis of chronic cystic mastitis and the type of material used in the studies. Moreover, in some of the investigations histologic confirmation of the clinical diagnosis was not carried out in all cases. The methods of analysis are also dissimilar. Warren's studies based on histologic examination demonstrate that when age specific rates are used, the breast cancer attack rate for women with chronic cystic mastitis in the premenopausal age group (from 30 to 49 years) is 11.7 times as great as that of the general female population in the same period. Past the age of 50 it is 2.5 times as great and for the entire group 4.5 times as great. Corrections were made for chronic cystic mastitis in the normal population. These findings are significant, since the group with the highest incidence was that in which the ovaries were still active. Therefore, if chronic cystic mastitis is of endocrine origin, then it must be postulated that hormones are responsible at least in an indirect fashion for the development of cancer of the breast.

#### *Hormonal Alteration of Tumors.—*

*Castration:* Herrell<sup>108</sup> reviewed the records of 1,906 patients with cancer of the breast and those of 1,011 without the disease in a similar age group. His findings disclosed that in the cancer group the incidence of complete oophorectomy or castration, before cancer was diagnosed, was 1.5 per cent. The incidence in the noncancer group was 15.4 per cent, or ten times as great. He also suggested that the time of castration was as important as in mice. Schinzinger<sup>109</sup> suggested oophorectomy as part of the treatment of breast cancer. Beatson<sup>110</sup> independently reported several patients who were castrated and noted alleviation of symptoms and signs. Many have since resorted to this procedure and in later years have substituted x-ray for surgical extirpation of the ovaries.<sup>111</sup> Benefits obtained were more striking in the premenopausal group, although even in this group the changes were usually temporary and except in one recorded instance did not show obvious regression of the primary tumor.<sup>112</sup> The greatest changes were noted in the bone metastases, which by x-ray evidence in a fair number of cases regressed or disappeared completely for a time. It has been concluded by those with an extensive experience that castration may be expected to show temporary improvement in about one-third of the patients with recurrent or inoperable cancer, but it cannot be demonstrated as advantageous when employed as a prophylactic procedure in those submitted to radical operation.<sup>113</sup> Farrow and Adair<sup>114</sup> have recently reported a similar experience concerning partial regression of the primary tumor and osseous metastases in a male with cancer of the breast. There can be no doubt that the changes resulted from removal of gonadal secretions. Whether this is the sole factor or whether the changes occur secondarily to an effect on the other glands of internal secretion following castration is a moot question.



The metabolic changes produced by the procedure must also be considered. Regarding x-ray castration, a study in this laboratory has revealed some discrepancy in its efficacy, when compared to the surgical operation.<sup>104</sup> It was found by assays of the urinary estrogen excretion that castration by x-ray, in order to simulate that by operation, depended upon such factors as adequate dosage, size of the portal, and age of the patient. Some patients, although amenorrheic, had a marked fluctuation of estrogens in the urine and in several instances resumed menstruation. Obviously, in this group castration was incomplete, so that results in such cases are equivocal.

*Menstrual Cycle:* As far as can be determined, there is no effect of the menstrual cycle on the primary tumor. There may be slight gross alterations in size of the tumor, but for the most part this is probably due to vascular change and edema rather than to alteration in epithelial activity.

*Pregnancy and Lactation:* The rapidity of growth of the primary tumor<sup>115</sup> and the appearance of a tumor in the second breast during pregnancy are well recognized.<sup>116</sup> Changes during lactation are usually even more striking.<sup>115</sup> Whether these effects are due to the hormones elaborated in pregnancy and lactation on the tumor, or to effects on the breast itself is not settled. Taylor and Meltzer,<sup>117</sup> as well as others,<sup>118</sup> contend that the structure of the breast late in pregnancy and during lactation favors development and growth of cancer, particularly with regard to the inflammatory type. This may be due to the increased vascularity which may favor tumor growth, to the richness of the lymphatics which favors dissemination, or to the relative absence of fibrous tissue which removes a natural barrier. These changes may all be produced by hormonal stimulation, but other products of pregnancy may also be responsible.

*Effect of Estrogens on the Development of Cancer of the Breast.*—Three reports have appeared on the possible development of cancer in the breast after prolonged administration of estrogens.<sup>119-121</sup> There is no proof that this was the direct cause of the tumor, but there is certainly a possibility that it was contributory. With the large numbers of females who are now receiving estrogens over long periods for various endocrine disturbances, particularly the menopause, one would expect the development of more cases if the hormone were directly responsible. However, when the life span, the time, and the dosage required to produce the lesion in a susceptible mouse are translated into human equivalents, it is possible that more cases will appear. In the case of Auchincloss and Haagensen<sup>120</sup> the effect of the estrogens seemed to resemble that seen in the mouse, and was of an unusual histologic type. They have cautioned against indiscriminate use of the hormone over a long period of time or in large doses, when there is a family history of cancer, without initial and repeated examination of both breasts, and in patients with chronic mastitis, cancer, or any form

of neoplasm either before or after surgical or radiation treatment. Such advice is valuable and should be considered by all those who use the hormones.

*Effect of Hormones on Cancer of the Breast.*—Attempts have been made to influence the course of cancer of the breast by the administration of hormones. We have been unable to demonstrate a direct effect with regard to either augmentation or inhibition of the primary tumor in mouse or man by the administration of estrogens or androgens. Farrow and Woodward<sup>122</sup> have noted that in the premenopausal group skeletal metastases are apt to occur early, whereas, in the postmenopausal group development of skeletal metastases is relatively late. They have also reported a marked acceleration of osseous metastases after intensive androgen or estrogen therapy and have suggested that there may be a direct effect on the secondary deposits themselves. An alternative theory is that these changes are due to an indirect effect which by removal of certain mechanical barriers possibly as a result of altered metabolism permits the metastases to grow unhampered. They, too, have considered this possibility. This is suggested by their observations of a marked decalcification of bone and a rise in concentration of calcium in the serum and excretion in the urine.

*Excretion Studies:* To date there have been relatively few studies on the excretion rates of the various sex hormones in patients with cancer of the breast. The results obtained thus far may be listed as follows:

**GONADOTROPIC HORMONE.**—There is no consistent alteration in the excretion of pituitary gonadotropic hormone in patients with cancer of the breast. Zondek<sup>123</sup> has reported an increased excretion of the gonadotropic hormone of placental origin in a pregnant woman with mammary cancer. He was of the opinion that it was due to the cancer as the values fell precipitously after radical operation in the eighth month of pregnancy. This finding in a single case seems to be equivocal.

**ESTROGENS.**—Ross and Dorfman<sup>124</sup> made several determinations on each of four patients in the premenopause with breast cancer and could detect no significant variation from normal. These findings have been corroborated by the study of a larger series by Taylor and Twombly<sup>125</sup> and by Nathanson.<sup>126</sup> The latter reported slightly lower values than normally found in some cases, whereas, others had normal or slightly elevated daily levels. In general, there was no deviation from normal, and although the average for the entire group was slightly below that of normal women of the same age, it was not considered significant. The excretion cycle of some of the patients appeared atypical in that the peak of estrogen excretion usually observed at the midmenstruum was either absent or delayed. The significance of such a configuration is equivocal. In cancer of the male breast, Yolton and Rea<sup>127</sup> have reported values comparable to that of normal males of the same age.

ANDROGENS AND 17-KETOSTEROIDS.—Normal androgen values were found by Ross and Dorfman<sup>124</sup> in their series. The excretion of 17-ketosteroids in the patients studied by Taylor and Twombly<sup>125</sup> and by Nathanson<sup>126</sup> were usually within normal range, but in general averages for the groups were slightly lower than those usually found for similar normal individuals. Pearlman<sup>128</sup> has reported a lowered 17-ketosteroid excretion in most patients with any type of cancer; these findings are in accord with those of others.<sup>129</sup> In the cancer of the male breast the 17-ketosteroid excretion has also been reported as normal.<sup>127</sup>

Taylor and Twombly<sup>125</sup> studied the effect of various steroid hormones on the excretion rates of the sex hormones in individuals with and without cancer of the breast. They concluded that there was no striking difference although variations did appear in the cancer patient.

Studies on patients in the menopause with cancer of the breast show essentially the same excretion rates as women in the same period without the disease. Several conclusions may be drawn from these excretion studies. (1) Although variations do occur, there is no significant deviation from normal in the excretion rates of the sex hormones in women with breast cancer. (2) There is no proof that abnormal secretions of the hormones do not accompany or precede the development of the cancer, since excretion levels are not absolute indicators of secretory activity. (3) Carcinoma of the breast may be independent of hormonal influence once it develops. (4) The findings do not prove that the sex hormones are not involved in the disease, but they do indicate that normal excretion values may be found in the presence of the cancer during the period of active ovarian function.

From the foregoing data, it can be concluded that there is no proof that the hormones are the direct cause of carcinoma of the breast. It is possible and likely in some cases that they are indirectly responsible, inasmuch as they may produce precancerous changes or may provide a suitable substrate so that another agent may act.

#### DISCUSSION

The available clinical and experimental information emphasizes the necessity for the endocrine system in the development and growth of the mammary gland. The ovary and hypophysis are especially important for without one or the other breast development will not occur or will cease entirely. Furthermore, removal of these organs leads to regressive changes in the fully developed breast. Thus, it has been contended that disease of the breast may be definitely related to or caused by alterations of function or secretion of certain of the glands of internal secretion. Factual data, for such a thesis, have been reviewed under each entity. However, a general discussion of the possibilities involved seems necessary since certain factors may be common to all types of breast disease.

*Status of the Individual.*—Factors other than endocrine must be considered in the development of breast disease. Chief among these are heredity, race, color, and constitutional type. They are frequently interrelated but each may be of special significance. While the evidence to support these possibilities is far from conclusive, one may justifiably speculate on them. The physiologic status of the individual, endocrine metabolism and secretion, and susceptibility to the disease may depend to a considerable degree on these fundamental backgrounds. These basic states in some measure may thus determine the type and degree of response of the organism to normal or superimposed stimuli. This would help to explain the variety of changes in the breast, which have been attributed to the same agent, such as estrogens.

The stage of life and state of the breast when abnormalities appear may, also, determine the type and degree of response to a given stimulus. It has been shown that the diseases which arise during various age periods vary considerably in their histologic structure and clinical manifestations. Moreover, the degree of development and structure of the breast may differ regardless of age as a result of changes in the physiologic status of the individual. Dieckmann<sup>28</sup> has shown that the extent of development of the breast particularly at puberty is subject to wide variation among different individuals. Previous pregnancies and normal and abnormal lactation account for breast changes not encountered in the virgin female. Other conditions, such as inflammatory disease may likewise alter the condition of the breast. Thus, the breast may exhibit wide varieties of histologic structure under different conditions. Hence, these dissimilar substrates may vary considerably in their response to a single stimulus and may determine to some degree the abnormal changes which may appear subsequently.

*Character of the Stimuli.*—Foremost among the probable stimuli which may be responsible for breast disease are those of the endocrine and nervous systems. The hormones which have been the subject of the most intensive study are the estrogens. Nevertheless, the possibilities suggested by investigations may apply to other hormones as well. How may estrogens produce these atypical states? Several possible modes of action seem tenable. (1) Physiologic amounts of the hormone may act upon tissue which is more sensitive than normal. This susceptibility may be related to the metabolic status of the host, to special characteristics of the cells, or to a change in the breast as a result of the activity of other agents. (2) It has been demonstrated that estrogens are destroyed by the liver. Normal quantities of the hormone may be secreted, but, because of defective function of the liver, abnormal quantities may be released to the tissues. (3) Excessive quantities of the hormone may be responsible, but, except in cancer-susceptible animals, the effects are limited. (4) Atypical hor-

mones may be produced, which may have carcinogenic activity. This is possible since the steroid hormones are closely allied to several of the known synthetic carcinogens. It is conceivable that the formation of carcinogenic agents from hormones may occur as a result of a faulty metabolism due to a change in the physiologic state of the host. (5) Lack of a hormone, which normally stimulates the breast, may lead to degenerative or regressive changes, which might then allow other agents to act.

As has been pointed out, the nervous system may also be involved. The action may be direct, but it is more likely that such stimuli may exert their effect by causing excesses or alterations of hormonal secretion. Then, too, the close interrelation of the various endocrine organs suggests that disturbance of one organ could affect the function of the others. Because of the possible methods of action or alterations of hormonal secretion, there is still lack of conclusive evidence to justify the acceptance of any one factor.

*Endocrine Dysfunction.*—In almost all types of breast disease from the simple infantile hypertrophy to the complex breast cancer, there is a suggestion of some dysfunction of the endocrine system in many of the cases. Thus far, the evidence has been confined almost entirely to clinical observations. To recapitulate, the relatively high incidence of atypical menstrual cycles, of disease of the female pelvic organs, of abnormalities of lactation, the fertility of the patients and the number of pregnancies, the time of life at which the various processes appear, and the accentuation or regression of several types of lesions after the appearance or removal of obvious stimuli is sufficient to point to the endocrine organs as possible etiologic factors. In the experimental animal, also, there are apparent differences in the endocrine constitution of the low and high mammary tumor strains. Some have reported differences in the estrous cycles, the fertility, changes in the breast following pregnancy, the histologic appearance of the glands of internal secretion (particularly the ovary and the adrenal), the response to known stimuli, and the time of life under identical conditions at which the tumors appear. The effect of one endocrine organ upon another must also be given serious consideration. Such analogies between men and animals are dangerous in drawing conclusions. Nevertheless, it can be stated at present that in either case there is no evidence to support the thesis that the hormones in themselves are directly responsible for the production of neoplastic disease. It is possible, however, that they may be the exciting factors in the production of precancerous lesions and in this fashion may contribute to the development of the malignant process.

*Significance of Hormone Excretion.*—Urinary excretion levels of the sex hormones represent only the end products of metabolism. It has not yet been proved, whether or not they give a true index of the

blood levels, the rate of secretion or destruction, or the utilization of the hormones by the tissues. Furthermore, they do not reveal the exact nature or relationship of the various components of the hormones excreted. Recent data from isolation studies suggest that patients with cancer may excrete estrogens<sup>120</sup> and 17-ketosteroids,<sup>129, 131</sup> in a different fashion from individuals without cancer. The usual relationship of the individual components of both the estrogens and 17-ketosteroids may be atypical, as well as the normal ratio between the total estrogenic and 17-ketosteroid complexes.

It is clear that alterations in excretion levels or the specific type of hormone isolated are not necessarily characteristic for patients with cancer. They may merely represent deviations from normal, which may occur only as a result of disturbed metabolism in the sick individual. They indicate, however, a distinct abnormality and as such are significant in the study of the disease.

*Similarity of Lesions of the Breast.*—As was previously suggested, the state of the breast at the time that an abnormal stimulation may be superimposed is probably of some importance. Infantile and virginal hypertrophy, early ripening, gynecomastia and mastitis in the male, and possibly adenofibrosis are remarkably similar in histologic appearance and in their resemblance to changes usually seen in the normal adolescent female. It is conceivable, therefore, that they may be due to the same etiologic agent, possibly the hormones. Lewis and Geschickter<sup>132</sup> have emphasized this similarity with respect to virginal hypertrophy, gynecomastia, and fibroadenoma, and there is fairly good evidence to support it. The different forms of cystic disease also basically resemble each other, in spite of considerable variation in the individual case. Each type may represent a further stage of a similar process. The more advanced forms such as Schimmelbusch's disease may conduce to, precede, or accompany carcinoma of the breast.

#### CONCLUSIONS

1. The endocrine organs and their secretions are necessary for normal growth, development, and maintenance of the mammary gland. As such, they are indirectly responsible for breast disease, inasmuch as they provide the tissue in which the lesions arise.

2. Factors such as heredity, constitution, race, color, and physiologic state of the individual must also be considered as etiologic factors in breast disease.

3. The state of the breast at the time of onset of disease seems to be an important factor in the type of lesion seen. A single stimulus may thus produce a variety of differently appearing lesions.

4. Localized tissue susceptibility may account for an unusual response to what may appear to be a normal stimulus.

5. Endocrine dysfunction is frequently associated with and may be responsible for certain benign lesions, but there is no absolute proof that it is the only or direct etiologic factor.

6. Hormones may possibly be the direct cause of malignant change in the breast either from an excess stimulation, or as a result of an atypical metabolism. As yet, there is no concrete evidence to prove this. It is more likely that they merely prepare a substrate upon which another agent may act.

#### REFERENCES

1. Cooper, A. P.: *Illustrations of the Diseases of the Breast*, Chap. IX, London, 1829, Longmans, Rees & Co.
2. Nelson, W. O.: Endocrine Control of the Mammary Gland, *Physiol. Rev.* 16: 488-526, 1936.
3. Turner, C. W.: *Sex and Internal Secretions*, Ed. 2, Chap. XI, Baltimore, 1939, Williams & Wilkins Company.
4. Werner, A. A., and Collier, W. D.: The Effect of Theelin Injections on the Castrated Woman, *J. A. M. A.* 100: 633-640, 1933.
5. MacBryde, C. M.: The Production of Breast Growth in the Human Female, *J. A. M. A.* 112: 1045-1049, 1939.
6. Geschickter, C. F., and Astwood, E. B.: The Relation of Oestrin and Other Hormones to Tumor Formation in the Breast, in: *Some Fundamental Aspects of the Cancer Problem*, New York, 1937, Science Press Printing Company, pp. 76-85.
7. Gardner, W. U., Smith, G. M., and Strong, L. C.: Stimulation of Abnormal Mammary Growth by Large Amounts of Estrogenic Hormone, *Proc. Soc. Exper. Biol. & Med.* 33: 148-150, 1935.
8. Burrows, H.: A Comparison of the Change Induced by Some Pure Oestrogenic Compounds in the Mammæ and Testes of Mice, *J. Path. & Bact.* 42: 161-168, 1936.
9. Van Heuverswyn, J., Folley, S. J., and Gardner, W. U.: Mammary Growth in Male Mice Receiving Androgens, Estrogens and Desoxycorticosterone Acetate, *Proc. Soc. Exper. Biol. & Med.* 41: 389-392, 1939.
10. Turner, C. W., and Frank, A. H.: The Effect of the Estrus-Producing Hormone on the Growth of the Mammary Gland, *Mo. Agr. Exp. Sta. Res. Bul.*, 145, 1930.
11. Astwood, E. B., Geschickter, C. F., and Rausch, E. O.: Development of the Mammary Gland of the rat, *Am. J. Anat.* 61: 373-405, 1937.
12. Turner, C. W., and Frank, A. H.: The Effect of the Ovarian Hormones Theelin and Corporin Upon the Growth of the Gland of the Rabbit, *Mo. Agr. Exp. Sta. Res. Bul.*, 174, 1932.
13. Selye, H., McEuen, C. S., and Collip, J. B.: Effect of Testosterone on the Mammary Gland, *Proc. Soc. Exper. Biol. & Med.* 34: 201-203, 1936.
14. Nelson, W. O., and Gallagher, T. F.: Some Effects of Androgenic Substances in the Rat, *Science* 84: 230-232, 1936.
15. Reece, R. P., and Mixner, J. P.: Effect of Testosterone on the Pituitary and Mammary Gland, *Proc. Soc. Exper. Biol. & Med.* 40: 66-67, 1939.
16. Van Wagenen, G., and Folley, S. J.: The Effect of Androgens on the Mammary Gland of the Female Rhesus Monkey, *J. Endocrinol.* 1: 367-372, 1939.
17. McCullagh, E. P., and Rossmiller, H. R.: Methyl Testosterone I. Androgenic Effect and the Production of Gynecomastia and Oligospermia, *J. Clin. Endocrinol.* 1: 496-502, 1941.
18. Riddle, O.: Lactogenic and Mammogenic Hormones, in: *Glandular Physiology and Therapy*, Chicago, 1942, American Medical Association, pp. 67-82.
19. Turner, C. W.: Present Status of the Mammogenic Hormone Theory, In: *The Ninth Annual Report of the International Cancer Research Foundation*, Philadelphia, 1941, pp. 140-143.
20. Riddle, O., Bates, R. W., and Dykshorn, S. W.: The Preparation, Identification and Assay of Prolactin—a Hormone of the Anterior Pituitary, *Am. J. Physiol.* 105: 191-216, 1933.

21. Gardner, W. U., and Turner, C. W.: The Function, Assay and Preparation of Galactin, a Lactation Stimulating Hormone of the Anterior Pituitary and an Investigation of the Factors Responsible for the Control of Normal Lactation, *Mo. Agr. Exp. Sta. Res. Bul.*, 196, 1933.
22. Gardner, W. U., and White, A.: Mammary Growth in Hypophysectomized Male Mice Receiving Estrogen and Prolactin, *Proc. Soc. Exper. Biol. & Med.* 48: 590-592, 1941.
23. Selye, H., Collip, J. B., and Thomson, D. L.: Nervous and Hormonal Factors in Lactation, *Endocrinology* 18: 237-248, 1934.
24. Cheattle, Sir G. L., and Cutler, M.: *Tumours of the Breast*, London, 1931, Edward Arnold & Co.
25. Taylor, H. C., Jr.: The Relation of Chronic Mastitis to Certain Hormones of the Ovary and Pituitary to Coincident Gynecological Lesions, *Surg., Gynec. & Obst.* 62: 129-148, 562-584, 1936.
26. Rosenberg, A.: Ueber Menstruelle, durch das Corpus Luteum Bedingte Mammaveraenderungen, *Frankfurt. Ztschr. f. Path.* 27: 466-506, 1922.
27. Ingleby, H.: Relation of Fibro-Adenoma and Chronic Mastitis to Sexual Cycle Changes in the Breast, *Arch. Path.* 14: 21-41, 1932.
28. Dieckmann, H.: Ueber die Histologie der Brustdruese bei Gestoertem und Undgestoertem Menstruationsablauf, *Virchows Arch. f. path. Anat.* 96: 1201-1205, 1931.
29. Nathanson, I. T., Towne, L. E., and Aub, J. C.: Normal Excretion of Sex Hormones in Childhood, *Endocrinology* 28: S51-S65, 1941.
30. Jung, F. T., and Shafton, A. L.: Mastitis, Mazoplasia and Gynecomastia in Normal Adolescent Males, *Illinois M. J.* 73: 115-123, 1938.
31. Nathanson, I. T., Aub, J. C., Farber, S., and Cutler, C. H.: The Generalized Effects of Hyperfunctioning Endocrine Tumors in Childhood, Reported at Third International Cancer Congress, Atlantic City, 1939. (To be published.)
32. Nathanson, I. T., and Aub, J. C.: Excretion of Sex Hormones in Abnormalities of Puberty, *J. Clin. Endocrinol.* 3: 321-330, 1943.
33. Friedgood, H. B., and Gargill, S. L.: Biochemical and Clinical Studies of Virilism Before and After Removal of Adrenal Cortical Tumor, *J. Clin. Investigation* 17: 504, 1938.
34. Geschickter, C. F.: Breast Pathology in Relation to Endocrine Disorders, in: *The Cyclopedia of Medicine*, Philadelphia, 1939, F. A. Davis, Company, pp. 543-571.
35. Taylor, H. C., Jr.: The Evidence for an Endocrine Factor in the Etiology of Mammary Tumors, *Am. J. Cancer* 27: 525-541, 1936.
36. Geschickter, C. F.: Estrogenic Mammary Cancer in the Rat, *Radiology* 33: 439-449, 1939.
37. Emge, L. A., and Murphy, K. M.: The Influence of Long-Continued Injections of Estrogens on Mammary Tissue, *Am. J. Obst. & Gynec.* 36: 750-768, 1938.
38. Kilgore, A. R.: Tumors and Tumor-like Lesions of the Breast in Association With Pregnancy and Lactation, *Arch. Surg.* 18: 2079-2098, 1929.
39. Geschickter, C. F., and Lewis, D.: Pregnancy and Lactation Changes in Fibroadenoma of the Breast, *Brit. M. J.* 1: 499-504, 1938.
40. Heiman, J.: The Influence of Androgenic Hormones on Transplanted Mammary Tumors in White Rats, *Am. J. Cancer* 39: 178-184, 1940.
41. Mohs, F. E.: The Transformation of Rat Mammary Adenofibroma to Fibroma by Androgens, *Cancer Research* 1: 151-153, 1941.
42. Nathanson, I. T.: Studies on the Etiology of Human Breast Disease II. Excretion of Estrogenic Hormone in Women With Fibroadenoma of the Breast (To be published).
43. Taylor, H. C., Jr.: Endocrine Aspects of Chronic Mastitis, *Surg., Gynec. & Obst.* 74: 326-342, 1942.
44. Semb, C.: Pathologico-anatomical and Clinical Investigations of Fibroadenomatosis Cystica Mammæ and Its Relation to Other Pathological Conditions in Mammæ, Especially Cancer, *Acta. chir. Scandinav. (Supp. 10)* 64: 1-484, 1928.
45. Taylor, H. C., Jr., and Waltman, C. L.: Hyperplasias of the Mammary Gland in the Human Being and in the Mouse, *Arch. Surg.* 40: 733-820, 1940.
46. Geschickter, C. F.: The Endocrine Aspects of Chronic Cystic Mastitis, *South. Surgeon* 10: 457-486, 1941.
47. Thorn, G., Nelson, K. R., and Thorn, D. W.: A Study of the Mechanism of Edema Associated With Menstruation, *Endocrinology* 22: 155-163, 1938.



48. Bucher, N. L. R., and Geschickter, C. F.: Corpus Luteum Studies. II. Pregnanadiol and Estrogen Output in the Urine of Patients With Chronic Cystic Mastitis, *J. Clin. Endocrinol.* 1: 58-64, 1941.
49. Nathanson, I. T.: Unpublished data.
50. Meigs, J. V., and Nathanson, I. T.: Unpublished data.
51. Nathanson, I. T., Meigs, J. V., and Parsons, L.: Studies on the Etiology of Mammary Pain and Secretion, Reported at the Third International Cancer Congress, Atlantic City, 1939.
52. Burrows, H.: Pathological Changes Induced in the Mamma by Oestrogenic Compounds, *Brit. J. Surg.* 23: 191-213, 1935.
53. Astwood, E. B., and Geschickter, C. F.: Changes in the Mammary Gland of the Rat Produced by Various Glandular Preparations, *Arch. Surg.* 36: 672-697, 1938.
54. Gilbert, J. B.: Studies in Malignant Testis Tumors. II. Syndrome of Choriogenic Gynecomastia, *J. Urol.* 44: 345-357, 1940.
55. Hunt, V. C., and Budd, J. W.: Gynecomastia Associated With Interstitial Cell Tumor of the Testicle, *J. Urol.* 42: 1242-1250, 1939.
56. Lissner, H.: A Case of Adrenal Cortical Tumor in an Adult Male Causing Gynecomastia and Lactation, *Endocrinology* 20: 567-569, 1936.
57. Levy Simpson, S., and Joll, C. A.: Feminization in a Male Adult With Carcinoma of the Adrenal Cortex, *Endocrinology* 22: 595-604, 1938.
58. Moehlig, R. C.: Pituitary Tumor Associated With Gynecomastia, *Endocrinology* 13: 529-532, 1929.
59. Glass, S. J., Edmondson, H. A., and Soll, S. N.: Sex Hormone Changes Associated With Liver Disease, *Endocrinology* 27: 749-752, 1940.
60. Klinefelter, H. F., Jr., Reifstein, E. C., Jr., and Albright, F.: Syndrome Characterized by Gynecomastia, Aspermatogenesis Without A-Leydigism, and Increased Excretion of Follicle-Stimulating Hormones, *J. Clin. Endocrinol.* 2: 615-627, 1942.
61. Starr, P.: Gynecomastia During Hyperthyroidism. Report of Two Cases, *J. A. M. A.* 104: 1988-1990, 1935.
62. Aub, J. C.: Personal communication.
63. Hoskins, W. H., Coffman, J. R., Koch, F. C., and Kenyon, A. T.: The Effect of Testosterone Propionate on the Urinary Excretion of Androgens and Estrogens in Eunuchoidism, *Endocrinology* 24: 702-710, 1939.
64. Dorfman, R. I., and Hamilton, J. B.: The Urinary Excretion of Estrogenic Substances After the Administration of Testosterone Propionate, *Endocrinology* 25: 33-38, 1939.
65. Nathanson, I. T., and Towne, L. E.: The Urinary Excretion of Estrogens, Androgens and F.S.H. Following the Administration of Testosterone to Human Female Castrates, *Endocrinology* 25: 754-758, 1939.
66. Nathanson, I. T., and Weisberger, D.: The Treatment of Leukoplakia Buccalis and Related Lesions With Estrogenic Hormone, *New England J. Med.* 221: 556-560, 1939.
67. Twombly, G. H.: Personal communication.
68. Dunn, C. W.: Stilbestrol Induced Gynecomastia in the Male, *J. A. M. A.* 115: 2263-2264, 1940.
69. Scarff, R. W., and Smith, C. P.: Proliferative and Other Lesions of the Male Breast, *Brit. J. Surg.* 29: 393-396, 1942.
70. Nathanson, I. T.: Studies on the Etiology of Human Breast Disease. I. Urinary Excretion of Follicle-Stimulating Hormone, Estrogens and 17-Ketosteroids in Adolescent Mastitis of Males, *J. Clin. Endocrinol.* 2: 311-314, 1942.
71. Nathanson, I. T.: Unpublished data.
72. Fevold, H. L., Fiske, V. M., and Nathanson, I. T.: Physiological Reactions Produced by Gonadotropic Hormones From the Urine of a Case of Chorioepithelioma, *Endocrinology* 24: 578-580, 1939.
73. Gardner, W. U.: Estrogens in Carcinogenesis, *Arch. Path.* 27: 138-170, 1939.
74. Loeb, L.: The Significance of Hormones in the Origin of Cancer, *J. Nat. Cancer Inst.* 1: 169-196, 1940.
75. Tyzzer, E. E.: A Study of Heredity in Relation to the Development of Tumors in Mice, *J. M. Research* 17: 199-211, 1907.
76. Slye, M.: The Incidence and Inheritability of Spontaneous Tumors in Mice (Second Report), *J. M. Research* 30: 281-285, 1914.
77. Little, C. C.: A Review of Progress in the Study of the Genetics of Spontaneous Tumor Incidence, *J. Nat. Cancer Inst.* 1: 727-736, 1941.

78. Lathrop, A. E. C., and Loeb, L.: Further Investigation on the Origin of Tumors in Mice. III. On the Part Played by Internal Secretion in Spontaneous Development of Tumors, *J. Cancer Research* 1: 1-20, 1916.
79. Loeb, L.: Further Investigations on the Origin of Tumors in Mice. VI. Internal Secretion as a Factor in the Origin of Tumors, *J. M. Research* 40: 477-496, 1919.
80. Cori, C. F.: Influence of Ovariectomy on the Spontaneous Occurrence of Mammary Carcinomas in Mice, *J. Exper. Med.* 45: 983-991, 1927.
81. Wooley, G., Fekete, E., and Little, C. C.: Mammary Tumor Development in Mice Ovariectomized at Birth, *Proc. Nat. Acad. Sc.* 25: 277-279, 1939.
82. Murray, W. S.: Ovarian Secretion and Tumor Incidence, *J. Cancer Research* 12: 18-25, 1928.
83. Murray, W. S.: Sex Hormones and Cancer, *Am. J. Cancer* 30: 517-526, 1937.
84. Bagg, H. J.: Further Studies on the Relation of Functional Activity to Mammary Carcinoma in Mice, *Am. J. Cancer* 27: 542-550, 1936.
85. Fekete, E.: A Comparative Morphological Study of the Mammary Gland in a High and Low Tumor Strain of Mice, *Am. J. Path.* 14: 557-578, 1938.
86. Lacassagne, A.: Apparition de Cancers de la Mamelle Chez la Souris Male, a des Injections de Folliculine, *Compt. rend. Acad. d. sc.* 195: 630-632, 1932.
87. Lacassagne, A.: Relationship of Hormones and Mammary Adenocarcinoma in the Mouse, *Am. J. Cancer* 37: 414-424, 1939.
88. Bittner, J. J.: Some Possible Effects of Nursing on the Mammary Gland Tumor Incidence in Mice, *Science* 84: 162, 1936.
89. Bittner, J. J.: Breast Cancer in Mice as Influenced by Nursing, *J. Nat. Cancer Inst.* 1: 155-168, 1940.
90. Twombly, G. H.: Breast Cancer Produced in Male Mice of the C57(Black) Strain of Little, *Proc. Soc. Exper. Biol. & Med.* 44: 617-618, 1940.
91. Noble, R. L., McEuen, C. S., and Collip, J. B.: Mammary Tumours Produced in the Rats by the Action of Oestrone Tablets, *Canad. M. A. J.* 42: 413-417, 1940.
92. Nathanson, I. T., and Andervont, H.: Effect of Testosterone Propionate on Development and Growth of Mammary Carcinoma in Female Mice, *Proc. Soc. Exper. Biol. & Med.* 40: 421-422, 1939.
93. Jones, E. E.: The Effect of Testosterone Propionate on Mammary Tumors in Mice of the C3H Strain, *Cancer Research* 1: 787-789, 1941.
94. Gardner, W. U.: Mammary Tumors in Mice Receiving Sex Hormones (Abstract), *Cancer Research* 10: 724, 1942.
95. Cramer, W., and Horning, E. S.: Adrenal Changes Associated With Oestrin Administration and Mammary Cancer, *J. Path. & Bact.* 44: 633-642, 1937.
96. Loeb, L., and Kirtz, M. M.: The Effects of Transplants of Anterior Lobes of the Hypophysis on the Growth of the Mammary Gland and on the Development of Mammary Gland Carcinoma in Various Strains of Mice, *Am. J. Cancer* 36: 56-82, 1939.
97. Nathanson, I. T., and Welch, C. E.: Life Expectancy and Incidence of Malignant Disease. I. Carcinoma of the Breast, *Am. J. Cancer* 27: 40-53, 1936.
98. Taylor, H. C., Jr.: The Coincidence of Primary Breast and Uterine Cancer, *Am. J. Cancer* 15: 277-279, 1931.
99. Lane-Clayton, C. E.: A Further Report on Cancer of the Breast, With Special Reference to Its Associated Antecedent Conditions, Report on Public Health and Medical Subjects, No. 32, London, 1936, Great Britain Ministry of Health.
100. MacDonald, I.: Mammary Carcinoma: A Review of 2,636 Cases, *Surg., Gynec. & Obst.* 74: 75-82, 1942.
101. Adair, F. E.: Etiological Factors of Mammary Cancer in 200 Women: Also a Control Study of 100 Normal American Women, *New York State J. Med.* 34: 61-68, 1934.
102. Fekete, E., and Green, C. V.: The Influence of Complete Blockage of the Nipple on the Incidence and Location of Spontaneous Mammary Tumors in Mice, *Am. J. Cancer* 27: 513-518, 1936.
103. Olch, I. Y.: The Menopausal Age in Women With Cancer of the Breast, *Am. J. Cancer* 30: 563-566, 1937.
104. Nathanson, I. T., Rice, C., and Meigs, J. V.: Hormonal Studies in Artificial Menopause Produced by Roentgen Rays, *Am. J. Obst. & Gynec.* 40: 936-945, 1940.
105. Lewis, D., and Geschickter, C. F.: The Relation of Chronic Cystic Mastitis to Carcinoma of the Breast, *Surg. Gynec. & Obst.* 66: 300-307, 1938.

106. Warren, S.: The Relation of "Chronic Mastitis" to Carcinoma of the Breast, Surg., Gynec. & Obst. 71: 257-273, 1940.
107. Logie, J. W.: Mastopathia Cystica and Mammary Carcinoma, Cancer Research 2: 394-397, 1942.
108. Herrell, W. E.: The Relative Incidence of Oophorectomy in Women With and Without Carcinoma of the Breast, Am. J. Cancer 29: 659-665, 1937.
109. Schinzinger: Quoted by Herrell.<sup>105</sup>
110. Beatson, G. T.: On the Treatment of Inoperable Cases of Carcinoma of the Mammary; Suggestions for a New Method of Treatment With Illustrative Cases, Lancet 2: 104-107, 162-165, 1896.
111. Ahlbohm, H.: Castration by Roentgen Rays as Auxiliary Treatment in Radiotherapy of Cancer Mammæ at Radiumhemmet, Acta radiol. 11: 614-633, 1930.
112. Clarkson, W., and Barker, A.: Five Year Cure of Mammary Carcinoma With Multiple Metastases to Bone, Am. J. Roentgenol. 36: 615-621, 1936.
113. Taylor, G. W.: Evaluation of Ovarian Sterilization for Breast Cancer, Surg., Gynec. & Obst. 68: 452-456, 1939.
114. Farrow, J. H., and Adair, F. E.: Effect of Orchidectomy on Skeletal Metastases From Cancer of the Male Breast, Science 95: 654, 1942.
115. Smith, F. R.: The Effect of Pregnancy on Malignant Tumors, Am. J. Obst. & Gynec. 34: 616-633, 1937.
116. Trout, H. H.: The Remaining Breast After Radical Removal of the Opposite Side for Carcinoma, Surg., Gynec. & Obst. 34: 630-632, 1922.
117. Taylor, G. W., and Meltzer, A.: "Inflammatory Carcinoma" of the Breast, Am. J. Cancer 33: 33-49, 1939.
118. Rosenthal, A. H.: Carcinoma of the Breast and Pregnancy, Am. J. Surg. 43: 142-144, 1940.
119. Allaben, G. R., and Owen, S. E.: Adenocarcinoma of the Breast Coincidental With Strenuous Endocrine Therapy, J. A. M. A. 112: 1933-1934, 1939.
120. Auchincloss, H., and Haagenen, C. D.: Cancer of the Breast Possibly Induced by Estrogenic Substance, J. A. M. A. 114: 1517-1523, 1940.
121. Parsons, W. H., and McCall, E. F.: The Role of Estrogenic Substances in the Production of Malignant Mammary Lesions, SURGERY 9: 780-786, 1941.
122. Farrow, J. H., and Woodward, H. Q.: The Influence of Androgenic and Estrogenic Substances on the Serum Calcium in Cases of Skeletal Metastases From Mammary Cancer, J. A. M. A. 118: 339-343, 1942.
123. Zondek, B.: Increased Excretion of Gonadotropic Hormone in a Pregnant Woman With Mammary Carcinoma, J. Clin. Endocrinol. 1: 782-783, 1941.
124. Ross, M., and Dorfman, R. I.: The Urinary Excretion of Estrogens and Androgens by Women With Carcinoma of the Breast, Cancer Research 1: 52-54, 1941.
125. Taylor, H. C., Jr., Mecke, F. E., and Twombly, G. H.: Estrogen and 17-Ketosteroid Excretion in Patients With Breast Carcinoma, Cancer Research 3: 180-192, 1943.
126. Nathanson, I. T.: Studies on the Etiology of Human Breast Disease. III. Urinary Excretion of Estrogens and 17-Ketosteroids in Pre-Menopausal Carcinoma of the Breast, Read at Thirty-Fourth Annual Meeting of the American Association for Cancer Research, Boston, 1942.
127. Yolton, N., and Rea, C.: Excretion of Androgens and Estrogens in Males With Mammary Carcinoma, Proc. Soc. Exper. Biol. & Med. 45: 54-55, 1940.
128. Pearlman, W. H.: Steroid Excretion in Cancerous and Noncancerous Persons: 17-Ketosteroids, Endocrinology 30: 270-276, 1942.
129. Dobriner, K., Rhoads, C. P., Lieberman, S., Hill, B. R., and Fieser, L. F.: Abnormal Alpha Ketosteroid Excretion in Patients With Neoplastic Disease, Science 99: 494-496, 1944.
130. Pincus, G., and Pearlman, W. H.: Steroid Excretion in Cancerous and Noncancerous Persons: Urinary Estrogens, Cancer Research 1: 970-974, 1941.
131. Pincus, G.: Steroid Excretion in Cancerous and Noncancerous Persons (Abstract), Cancer Research 2: 729, 1942.
132. Lewis, D., and Geschickter, C. F.: Gynecomastia, Virginal Hypertrophy and Fibroadenoma of the Breast, Ann. Surg. 100: 779-795, 1934.

## THE EFFECT OF SEX HORMONES ON SKELETAL METASTASES FROM BREAST CANCER

JOSEPH H. FARROW, M.D., NEW YORK, N. Y.

(From the Breast Department, Memorial Hospital)

IN THE medical literature there are reports of almost every type of human cancer metastasizing to the skeletal system. It is well known, however, that cancers originating in certain organs rarely metastasize to bone while others seem to have a selective proclivity for the osseous parts. This peculiar variation does not seem to be determined by the simple laws of chance or the proximity of the primary growth to the bony structures; it suggests contributing factors of local and systemic origin. From an endocrinological viewpoint it appears especially significant that the two primary cancers most frequent to metastasize to bone arise in the breast and prostate, organs whose development and functions are closely allied with the metabolism of sex hormones. Hence, among the many measures tried to control primary and metastatic cancer of the breast and prostate is the artificial production of a hormone imbalance.

An investigation of the effect of ovarian estrogens and testicular androgens on mammary cancer and its metastases to bone presents a most complex problem, one subject to many controversial opinions as well as conflicting clinical data. It is therefore necessary to preface this presentation with certain fundamentals in order to facilitate a systematic review and an intelligent interpretation of the variable results.

*First*, the ovaries and the testes are a part of the endocrine system. The organs of this system and their individual products show a remarkable degree of normal variation as well as multiplicity of effect, and yet by an integral relationship with each other maintain a hormonal balance to which the system tends to revert. Hence, any natural or artificial disturbance of this balance, caused by either the menopause or castration, will be followed by compensatory changes in other endocrine organs and a partial replacement by hormones or compounds having a biologic effect similar to that of those which have become deficient. Thus, Woolley, Fekete, and Little<sup>1</sup> report a nodular hyperplasia of the adrenal cortex and subsequent proliferation of the mammary epithelium following castration of both male and female mice. Furthermore, in an extensive review of experimental work, Riddle<sup>2</sup> notes that hormones capable of producing growth of the breast tissues have been found not only in the ovary but in the pituitary, adrenal,

*Treatment.*—The patient was treated solely by ovarian irradiation. This was begun Aug. 14, 1940, and completed eight days later. Using 200 kilovolts,  $\frac{1}{2}$  cm. copper filter, 70 cm. skin target distance, 500 roentgens were given daily to one of four pelvic fields for a total of 1,000 r to each area.

*Clinical Observations.*—During the month following pelvic irradiation she had a scant menstrual flow on three occasions. Then she began having fairly severe menopausal symptoms and had no further menstrual bleeding. There was a gradual decrease in the hyperemia of the cutaneous nodules. This was later followed by their shrinkage and at the end of ten months the nodules were barely palpable.

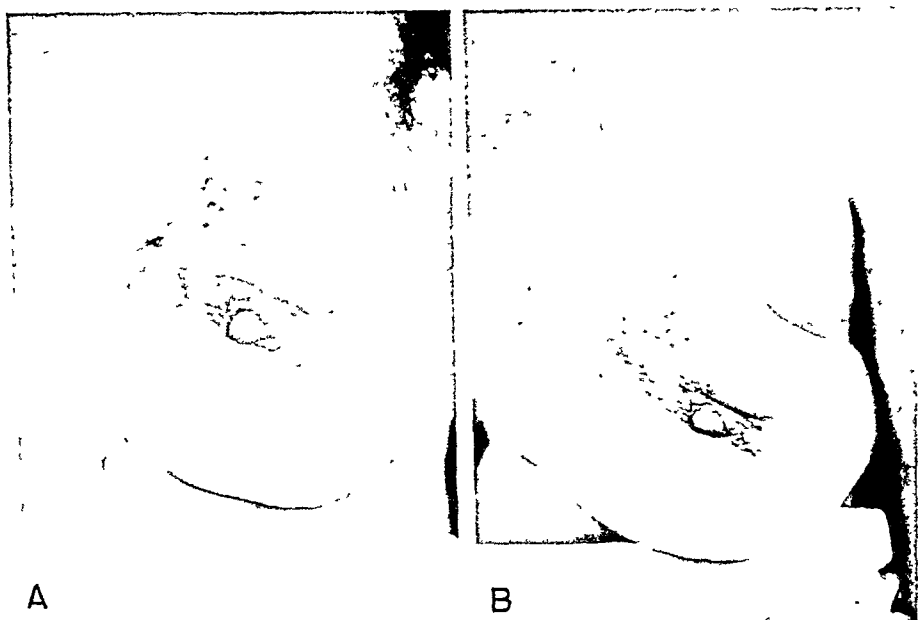


Fig 1 (Case 1).—A. Photograph taken shortly after menstruation ceased because of pelvic irradiation; B, 16 months later. Note disappearance of cutaneous nodules and marked decrease of lymphoedema of skin of breast.

One year following castration axillary nodes could not be definitely felt and the mass in the breast was estimated to be about one-third of its original size. She had gained considerable weight and had no symptoms suggestive of distant metastases. The last clinical examination nineteen months after castration revealed evidence of renewed disease activity by the appearance of two new skin nodules.

The pertinent points were a visible loss of vascularity of the lesions and their gradual shrinkage until no longer palpable. Skin nodules for histologic studies were removed 26, 71, and 234 days following castration. All of them showed apparently unaltered cancer cells, although the lesions were decreasing in size. From this evidence it is believed that the regression was due mainly to vasoconstriction causing a nutritional anemia and abortive fibrosis. Although no similar studies have been made on skeletal metastases following castration, I have made certain observations which lend some support to this view. First, osteoplastic lesions from breast cancer rarely appear in the pre-menopausal group unless the patient has been sterilized. Second, it

has been noted that osteolytic lesions occurring in varicular bones such as the ribs, vertebrae, and pelvis show comparatively early calcification after castration whereas those of the shaft of the long bones may show only minor changes. Moreover, in comparing the rate of calcification of medullary metastases with the clean-cut or "punched out" cortical ones, it is apparent that those in the medullary part of the bone show increased density more rapidly.

#### ADDITION OF ESTROGENS

There is a wealth of excellent experimental data in the literature on the appearance of breast cancer in both male and female animals after the administration of estrogenic substances. Fortunately, the number of reported cases of human cancer which follow or at least appear in time after the injection of female sex hormones is limited. The reports of Auchincloss and Haagensen,<sup>11</sup> Allaben and Owen,<sup>12</sup> and Parsons and McCall<sup>13</sup> are cautious in their conclusions but certainly warrant the timely editorial of the *Journal of the American Medical Association*<sup>14</sup> warning against the indiscriminate use of estrogenic substances for mammary disease.

There are surprisingly little experimental data on the effect of estrogenic substances on an established cancer in animals. Haddow,<sup>15</sup> after a limited number of observations in mice, reports no inhibition of growth.

For clinical data one can always bring forth the much discussed and controversial question of the effect of pregnancy on breast cancer. The reports are confusing, mainly because the material is limited and no one has observed a sufficient number of untreated breast cancers associated with pregnancy to warrant conclusions. There is certainly no evidence that pregnancy inhibits the growth of cancer. Smith,<sup>16</sup> from studies at the Memorial Hospital, did not believe that pregnancy materially influenced the course of breast cancer. Riach,<sup>17</sup> Rosenthal,<sup>18</sup> and Emge,<sup>19</sup> from much less clinical data, believed that pregnancy definitely accelerated the growth of breast cancer in their cases. The report of Ego-ville<sup>20</sup> is of particular interest. His patient, aged 30 years, had as her first symptom pain in the back beginning in the sixth month of pregnancy. Clinical and radiographic examinations demonstrated a cancer of the breast with widespread bone metastases. The blood showed a serum calcium level of 18.7 mg. per 100 c.c. Studies of the blood showed a serum calcium level of 18.7 mg. per 100 c.c. The patient failed rapidly and died.

I have observed the effect of estrone on skeletal metastases from breast cancer in only three instances. Unfortunately, for the purposes of the present analysis, these patients had previously received large doses of testosterone propionate. Therefore, the clinical effect of this estrone is greatly reduced and requires further substantiation. The estrone administered parenterally were relatively small doses.

given 2 and 4 mg. while the remaining two had only single doses of 2 mg.

The case here mentioned will illustrate the elevation of the serum calcium following injections of estrone as well as testosterone propionate.

CASE 2.—Oct. 21, 1939, Miss L. L., aged 26 years, was admitted to Memorial Hospital. She complained chiefly of a severe and persistent pain in the thoracic spine of two and one-half months' duration. For one year she had been aware of a small growth in the right breast. There had been a weight loss of seventeen pounds but no other associated systemic disturbances. Menses were regular with the flow lasting about six days. An examination of the right breast revealed a  $4$  by  $3\frac{1}{2}$  by  $2\frac{1}{2}$  cm. tumor. It was located in the upper central portion of the breast. In the adjacent midaxilla there was a metastatic node 1 cm. in diameter. Roentgenographic studies demonstrated osteolytic lesions in the ribs, spine, cranium, and pelvic bones. Aspiration biopsy of the breast tumor was reported cancer.

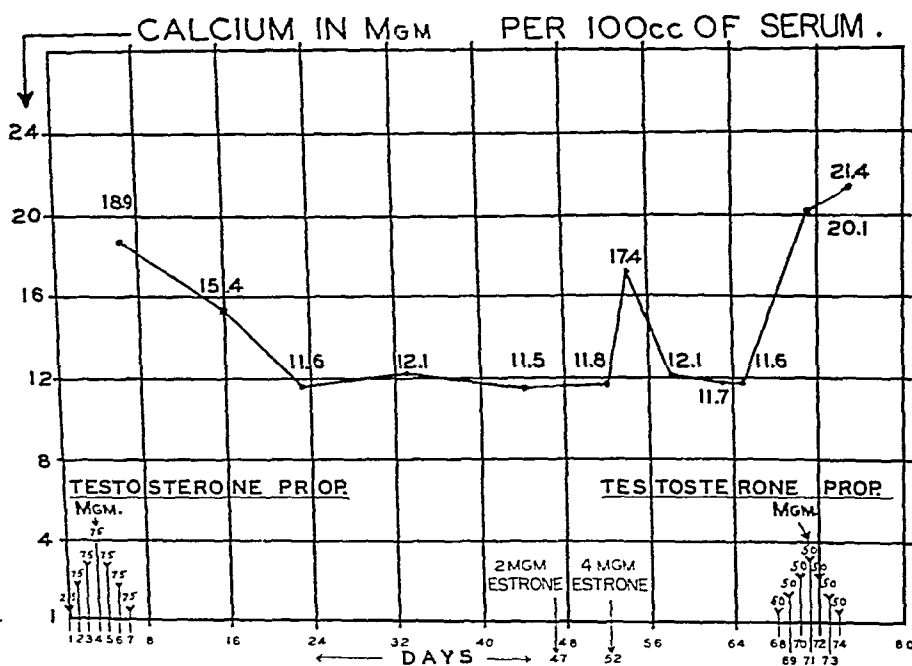


Fig. 2 (Case 2).—Demonstrating the elevation of the serum calcium following injections of testosterone propionate and estrone.

**Treatment.**—The patient was admitted to the Memorial Hospital and 25 mg. of testosterone propionate in 1 c.c. of sesame oil were injected into the gluteal muscle. During the following six consecutive days the dose was increased to 75 mg. daily, making a total of 475 mg. in seven days. Six weeks later she was given 2 mg. of estrone in oil intramuscularly and after an interval of five days an additional 4 mg. Nine days later a second series of testosterone injections was started, 50 mg. daily being given for a total of seven doses.

**Clinical Observations.**—After each series of injections the patient suffered from nausea and vomiting which subsided a few days after discontinuing the administration of the hormones. In general the clinical course of this patient was one of progressively failing health owing to widespread and uncontrolled metastatic disease. She died Jan. 17, 1940.

Of particular interest was the appearance of hypercalcemia (Fig. 2) after each series of hormone injections. During the period of observation a slight increase in the size of the breast tumor was noted. Roentgen studies demonstrated a striking increase in the extent of the osteolytic metastases in the ribs, spine, and pelvic bones.

Concerning the effects of estrone as well as testosterone it is assumed with probability that the resulting hypercalcemia was due mainly to an increased activity of the metastatic tumor in the skeletal system. This in turn caused an acceleration in the rate of bone destruction accompanied by a flooding of the circulation by the products of osteolysis.

Not infrequently one is faced with the problem of giving estrogens to postmastectomy patients who are suffering from menopausal disturbances. While there is no clinical evidence to contraindicate estrogenic therapy in the absence of disease, it is highly important to consider the possibility of activating a quiescent and unrecognized focus of metastatic cancer. In general it would be much safer to forbid pregnancy or the use of estrogens in all cases of mammary cancer for at least five years and preferably longer.

#### ADDITION OF ANDROGENS

It has been only within the past five years that the production of the primary male sex hormone, testosterone propionate, has been sufficient to permit experimental and clinical use. During this time there have been reports stressing the inhibitory action of this substance on the growth and function of the mammary gland.

The effect of testosterone on breast cancer has received only limited attention. Nathanson and Andervont<sup>21</sup> found that when testosterone was given to mice of the C3H strains at an early age it prevented the development of spontaneous tumors. They added, however, that no effect could be observed on the growth of a tumor already present. More recently, Loeser<sup>22</sup> has reported that the implantation of testosterone pellets in mice of the Strong A strain reduced the mortality from spontaneous cancer from 75 per cent in the controls to 40 per cent in the treated animals.

Loeser<sup>22</sup> also reports on the use of testosterone in five human beings with cancer. Three of these were said to be free of disease at the time the pellets were implanted and remained well for almost four years. In two cases where disease was present no regression of the cancer was observed although systemic improvement and relief of pain were noted.

Beginning in 1939, a series of thirty-three patients having bone metastases from breast cancer was given doses of testosterone propionate varying from 5 to 25 mg. in sesame oil for totals of six to twelve doses. All of these patients are now dead. Temporary relief from pain with some general improvement was noted in about one-half of the cases. No case showed clinical or radiographic evidence of disease control.



Later three females and one male were given large doses of testosterone propionate. A complete report<sup>5</sup> has been published on the three female patients. One of these cases has already been cited elsewhere in this article. The remaining two women were aged 37 and 60 years, respectively, and had developed bone metastases after radical mastectomies. The younger of these two patients was given 400 mg. of male sex hormone at the rate of 25 mg. twice daily. By the fifth days after the injections the serum calcium had risen from an initial level of 11.6 mg. to 15.4 mg. The other patient received two 25 mg. ampules of testosterone daily for ten days. Her serum calcium increased from 10.2 to 14.2 mg. Both patients also received 2 mg. of estrone several weeks after the injections of the male sex hormone. This too was followed by a similar but less marked hypercalcemia. The clinical course of the two women was relatively the same. Both failed rapidly and died. X-ray studies of the bones revealed further extension of previous metastases and the appearance of numerous new ones.

The fourth case, that of a male, is briefly summarized below.

CASE 3.—In May, 1939, Mr. J. S., aged 63 years, applied to the Memorial Hospital for treatment of a progressive swelling of the left breast of ten months' duration and persistent pains in the right thigh for the previous three months. An examination of the left breast demonstrated an ulcerating cancer, centrally located and measuring 4.5 cm. in diameter. A hard metastatic node having a diameter of 3.5 cm. was present in the adjacent axilla. X-rays of the pelvis showed osteolytic metastases in the upper right femur. Biopsy of the breast lesion was reported, "Adenocarcinoma—tubular duct, Grade II."

Treatment consisted of high voltage x-ray therapy to the breast, axilla, and right femur. Later a palliative simple mastectomy was performed. Pains in the hip were immediately relieved but recurred within seven months. He was readmitted to the hospital and given daily injections of 50 mg. of testosterone propionate for seventeen consecutive days except for two days when 100 and 75 mg. were given. A total of 925 mg. was administered during the seventeen days.

*Clinical Observations.*—The pains were not relieved. He complained of nausea on several occasions but suffered no vomiting. Following discharge from the hospital pain became more severe and on the thirty-fourth day after hormone therapy x-ray studies of the skeletal system indicated widespread metastases. Previously seen foci had shown marked extension and numerous new areas were present. Subsequently x-ray therapy was given with only slight relief. Prior to death ten months later he suffered numerous pathologic fractures.

The main points to be emphasized are a rapid extension of pre-existing skeletal metastases and the appearance of numerous new ones. Although there were no marked blood chemical changes, hormone studies of the urine during the time of treatment showed an increase in the output of estrogens (34.0 to 50.0 M.U.) and of androgens (44.5 to 56.7 mg.).

From this evidence it is apparent that the administration of large doses of synthetic androgens not only failed to inhibit the growth of metastatic mammary cancer but seemed to increase its activity in the skeletal system in both sexes.

## WITHDRAWAL OF TESTICULAR ANDROGENS

Male breast cancer is relatively uncommon, comprising about 1 per cent of all mammary cancers. From collected reviews,<sup>23-25</sup> however, it is apparent that there are no recognized histologic differences and the clinical course is relatively the same in both sexes.

Mainly because of the sequence of events described in Case 3 another male with breast cancer with skeletal metastases was treated by castration. Since it is to be reported elsewhere only a brief summary follows.

CASE 4.—M.S., aged 72 years, applied to the Memorial Hospital on April 28, 1941. Four months previously he had noticed an ulceration of the left nipple. This had not only refused to heal but had become larger. An examination revealed an ulcerating cancer which had destroyed the nipple. It measured 5 by 4 by 2½ cm. and was movable. Several nodes were palpable in the left axilla,



Fig. 3 (Case 4).—Roentgenogram demonstrating osteolytic metastases in the right ilium and pubic bones as well as the fourth lumbar vertebra.

the largest of which measured 1 cm. in diameter. The chest plate was negative. A radical mastectomy was advised but refused by the patient, who did not return to the hospital until nine months later. During the interval there had been a definite increase in the size of the local lesion. For several weeks he had suffered persistent pains in the right chest and the back. X-rays showed numerous metastases in the ribs, spine, pelvis, scapula, and skull. There was also fluid in the left pleural cavity interpreted as indicative of probable pulmonary metastases. A biopsy of the breast lesion was reported, "Infiltrating mammary carcinoma, Grade II."

*Treatment.*—The patient was admitted to the hospital and a bilateral orchidectomy performed Feb. 9, 1942.

*Clinical Observations.*—Relief of pain was almost immediate. Subsequent clinical and radiographic examinations have revealed a regression of the breast tumor with partial healing of the ulceration and also an increased density of the pre-existing skeletal lesions. The latter was most marked in the ribs, ilium, scapula, and lumbar vertebrae. The fluid in the left pleural cavity had disappeared.



Fig. 4 (Case 4).—Roentgenogram taken four months following castration. Note increased density of metastatic foci in the right ilium and fourth lumbar vertebra.

Blood chemical studies on this patient revealed no significant changes except an elevation of the acid phosphatase from 0.15 to 1.0 units. Hormone analysis of the urine indicated a decrease in the estrogen excretion from 22.5 to less than 4 M.U. while the output of 17 ketosteroids remained fairly stable.

While the interval of four months does not permit any definite conclusions, the evidence at hand indicates a regression of both the local lesion and the osseous metastases. It is highly probable that this is temporary.

#### CONCLUSIONS

At present any attempt to describe the possible effect of natural or synthetic endocrine products on the growth of primary or metastatic breast cancer means merely the recording of one or several observations. The fact remains that present knowledge is far from complete. To summarize, it appears that estrogens and androgens have a similar effect on skeletal metastases from mammary cancer. The evidence at this time indicates growth inhibition in certain cases following a withdrawal of either of these hormones. Conversely, an excess of either

seems to accelerate the rate of growth. Furthermore, it is highly probable that the observed effects are inconstant and of a temporary nature.

## REFERENCES

1. Woolley, G., Fekete, E., and Little, C. C.: Effect of Castration in the Dilute Brown Strain of Mice, *Endocrinology* 28: 341-343, 1941.
2. Riddle, Oscar: Lactogenic and Mammogenic Hormones, *J. A. M. A.* 115: 2276-2281, 1940.
3. Farrow, Joseph H., and Woodard, Helen Q.: Influence of Androgenic and Estrogenic Substances on the Serum Calcium in Cases of Skeletal Metastases From Mammary Cancer, *J. A. M. A.* 118: 339-343, 1942.
4. Beatson, G. T.: On the Treatment of Inoperable Cases of Carcinoma of the Mammary: Suggestions for a New Method of Treatment, With Illustrative Cases, *Lancet* 2: 104-107, 162-165, 1896.
5. Lett, Hugh: An Analysis of 99 Cases of Inoperable Carcinoma of the Breast Treated by Oophorectomy, *Lancet* 1: 227-228, 1907.
6. Dresser, Richard: The Effect of Ovarian Irradiation on the Bone Metastases of Cancer of the Breast, *Am. J. Roentgenol.* 35: 384-388, 1936.
7. Taylor, Grantley W.: Evaluation of Ovarian Sterilization for Breast Cancer, *Surg., Gynec. & Obst.* 68: 452-456, 1939.
8. Smith, E. G.: Sterilization in Carcinoma of the Breast, *Am. J. Roentgenol.* 36: 65-72, 1936.
9. Martin, Charles L.: The Relation of the Endocrine System to Malignancy, *Am. J. Roentgenol.* 36: 314-323, 1936.
10. Clarkson, Wright, and Barker, Allen: Five Year Cure of Mammary Carcinoma With Multiple Metastases to Bone, *Am. J. Roentgenol.* 36: 615-621, 1936.
11. Auchincloss, Hugh, and Haugen, Cushman D.: Cancer of the Breast Possibly Induced by Estrogenic Substance, *J. A. M. A.* 114: 1517-1523, 1940.
12. Allaben, G. R., and Owen, S. L.: Adenocarcinoma of the Breast Coincidental With Strenuous Endocrine Therapy, *J. A. M. A.* 112: 1933-1934, 1939.
13. Parsons, Willard H., and McCall, Eugene P.: The Role of Estrogenic Substances in the Production of Malignant Mammary Lesions, *SURGERY* 9: 780-786, 1941.
14. Editorial: Contra-indications to Estrogen Therapy, *J. A. M. A.* 114: 1560-1561, 1940.
15. Haddow, Alexander: Influence of Carcinogenic Compounds and Related Substances on the Rate of Growth of Spontaneous Tumors of the Mouse, *J. Path. & Bact.* 47: 567-578, 1938.
16. Smith, Frank R.: The Effect of Pregnancy on Malignant Tumors, *Am. J. Obst. & Gynec.* 34: 616-633, 1937.
17. Riach, Jean S.: Carcinoma of the Breast Complicated by Pregnancy, *M. Woman's J.* 46: 306-309, 1939.
18. Rosenthal, Alexander H.: Carcinoma of the Breast and Pregnancy, *Am. J. Surg.* 43: 142-144, 1939.
19. Emge, L. A.: The Influence of Pregnancy on Tumor Growth, *Am. J. Obst. & Gynec.* 28: 682-697, 1934.
20. Ego, J. W.: Metastatic Calcification in a Case of Carcinoma of the Breast, *Arch. Path.* 26: 1047-1051, 1938.
21. Nathanson, Ira T., and Andervont, Howard B.: Effect of Testosterone Propionate on Development and Growth of Mammary Carcinoma in Female Mice, *Proc. Soc. Exper. Biol. & Med.* 40: 421-422, 1939.
22. Loeser, Alfred A.: Mammary Carcinoma, Response to Implantation of Male Hormone and Progesterone, *Lancet* 241: 698-700, 1941.
23. Sachs, Maurice D.: Cancer of the Male Breast, *Radiology* 37: 458-467, 1941.
24. Gilbert, Judson B.: Cancer of the Male Breast With Special Reference to Etiology, *Surg., Gynec. & Obst.* 57: 451-466, 1933.
25. Wainwright, J. M.: Carcinoma of the Male Breast, *Arch. Surg.* 14: 836-859, 1927.

# BENIGN HYPERTROPHY AND CARCINOMA OF THE PROSTATE

## OCCURRENCE AND EXPERIMENTAL PRODUCTION IN ANIMALS

ROBERT A. MOORE, M.D., ST. LOUIS, MO.

(From the Department of Pathology, Washington University School of Medicine, St. Louis)

THE basic observation that the testes control the development and state of the secondary sexual organs was made at some time early in the history of man's contact with domesticated animals, either accidentally or deliberately. The farmer used this information in the castration of roosters to produce capons, with their supposed greater weight and more delicious meat. Castration of other animals was also found to be useful to the agriculturist. In man, the Turks and Chinese took advantage of the suppression of secondary sexual characters and sexual drive by orchietomy in prepuberal boys to supply the eunuchs for the harems. Religious sects, such as the Scopzen in Russia, used gonadectomy in the male to depress sexual drive after the thirty-fifth year of life as a part of their taboo. Incidentally, the operation of ovariectomy was beyond their ability, so that the comparable procedure in women was to sew the labia almost closed and burn the nipples.

Scientific study of the phenomenon of atrophy of the secondary sexual characters after the removal of the testes was initiated by John Hunter, who noted among other things that the prostate underwent progressive atrophy. This knowledge of a general biologic principle was put to little practical use in the treatment of disease in man until the end of the nineteenth century, when White proposed that castration be used to induce atrophy of the enlarged prostate of older men. Within the last few years Huggins and his associates have shown that the testes in some way influence the growth of prostatic carcinoma, and that removal of them results in considerable clinical improvement.

It is the purpose of this communication to present the evidence for and against the concept that benign hypertrophy and carcinoma of the prostate are endocrinologic dystrophies, and to review the occurrence and experimental production of the two conditions in animals.

### EVIDENCE THAT BENIGN HYPERTROPHY OF THE PROSTATE IS AN ENDOCRINOLOGIC DYSTROPHY

*Age Incidence.*—Benign hypertrophy of the prostate is characteristically a disease of men over the age of 40 years. Few if any patients with true nodular hyperplasia have been observed before this age. Most

The experimental investigations reported in this paper were supported by grants from the Daniel and Florence Guggenheim Foundation, the Roger and Gladys Straus Foundation, and the Josiah Macy Junior Foundation.

Received for publication, Sept. 28, 1943.

instances of prostatism in younger men are the result of acute prostatitis or of hypertrophy of the median bar of muscle at the internal urethral orifice. In my own series of over 700 prostates studied microscopically, the youngest individual with a true nodule formed within the prostatic tissue was 39 years of age, and the nodules in this case were microscopic in size. With increasing age there is an increasing incidence of benign hypertrophy, until 75 per cent of all men from 80 to 90 years of age have histologically demonstrable nodules within the gland (Moore). In contrast with this, the clinical incidence of urethral obstruction demanding operative interference reaches a maximum at about the age of 63 years (Gover). It is possible that patients older than 63 years are not subjected to operative removal of the enlarged prostatic tissue, but a number of urologists have told me that this cannot be the entire explanation. In terms of the etiologic agent these figures mean that the causal agent is present after the age of 40 years, that it reaches its greatest intensity at the age of about 60 years, and decreases in intensity thereafter, but remains active in the production of additional and new nodules.

*Racial Incidence.*—A difference in racial incidence does not of necessity mean that a disease is caused by a hormonal dystrophy, but it does establish a constitutional difference. In contrast with the figures noted for the Caucasian race, benign hypertrophy of the prostate, both clinically and pathologically, is a rare disease among the Chinese people (Chang and Char). Comparative figures are 45 to 55 per cent of all Caucasian men over 40 years of age, and 6 per cent of similar Chinese men. Char\* informs me that he has no explanation of this difference except one of constitution. It is true that Buddhist religion prohibits sexual intercourse after the age of 35 years, but it is improbable that this is held to by all Chinese people, and as will be explained in the next paragraph this could not account for the entire difference. In contrast, hypertrophy of the prostate in Negroes is as common as in the white man (D'Aunoy, Schenken, and Burns; Derbes, Leche, and Hooker).

*Marital State.*—According to the extensive investigation of Gover, benign hypertrophy of the prostate is slightly less common in single men than in married men, when the marital state of patients with the disease is compared with the marital state of the population in general. This difference is significant, with a probable error in excess of 4. Young suggests that benign hypertrophy is a rare disease in the Catholic hierarchy, but Dr. Edward L. Keys of New York informs me that he has seen many priests of the Catholic Church with the condition, and believes that it is as common in them as in the general population.

*Constitution.*—There are no precise scientific studies on the relation of constitution to the incidence of benign hypertrophy. It has been suggested that men whose constitutions tend toward the feminine type—that is, men with broad hips, prominent breasts, inconspicuous sexual hair,

\*Professor of Urology at the Peking Union Medical College.

and loose inguinal rings—develop benign hypertrophy more frequently than others (Moszkowicz). Draper found that individuals with benign hypertrophy had longer ears than any other group of individuals with disease. There is a single report of the occurrence of benign hypertrophy in identical twins in the same year of life (Kaufmann).

*Retention of Exogenous Creatine.*—It has been postulated that the retention of ingested or injected exogenous creatine is an index of the state of androgenic stimulation. Studies of young individuals, older men without disease of the prostate, and older men with prostatic hypertrophy reveal no difference in the retention of exogenous creatine. By injection of androgens into all of these individuals there is increased retention, indicating that the tissues are still responsible to the androgenic hormones (Sutton).

*The Effect of Castration.*—At the end of the nineteenth century White proposed that since the prostate undergoes atrophy following castration, the enlarged prostate should also undergo atrophy. The procedure was carried out on a large number of patients, but the evaluation of the results became so controversial that it is not possible at the present time to evaluate them with any accuracy. In the original report by Young on perineal prostatectomy, there are descriptions of the prostates of two individuals subjected some years before to castration. The typical hyperplasia of the epithelium and of the stroma is described in both. The slides on the case reported by Nanerode have been kindly reviewed for me by Dr. C. V. Weller,\* and his description is typical of benign hypertrophy without evidence of atrophy. Similarly, in one case in the files of the New York Hospital, I have not been able to find any evidence that castration brings about atrophy of the hyperplastic tissue. More recently, Deming, Jenkins, and van Wagenen came to the same conclusion. Deming has been good enough to allow me to examine the sections, and I fully agree with his interpretation. In contrast, Huggins and Stevens have examined two enlarged prostates several months after castration, and in one case found atrophy of the epithelium and of the stroma. Huggins has given me slides from this case, and I find myself in full agreement with his interpretation. It is entirely possible that a few patients respond and that most do not. Certainly the subject is worthy of further investigation.

*The Effect of Hormones.*—Most reports of the study of tissues in prostatic hypertrophy following the injection of androgens leave no doubt that these substances have no effect on the histologic appearance of the hyperplastic tissue (Moore and McLellan; Draper, Slaughter, and Denslow; Heckel). There is a single report that additional hyperplasia was present (Keller and Hull). With estrogens there are the typical changes resulting in all animal species: metaplasia of the urethral and ductal epithelium and increase of lymphoid tissue (Moore and McLellan). In-

\*Professor of Pathology at the University of Michigan.

investigators at the Cleveland Clinic, working under the general direction of Lower, found that castration in rats resulted in atrophy of the prostate and hypertrophy of the pituitary gland. Injections of androgens restored the prostate to normal but had no effect on the pituitary. On the other hand a water-soluble extract of the testes induced atrophy of the prostate but restored the pituitary to normal. They therefore postulated that the testes contained two hormones, one fat-soluble and one water-soluble. Feeding of the latter substance to patients with benign hypertrophy resulted in clinical improvement in about 60 per cent. Reed Nesbit\* has been good enough to allow me to examine sections from the prostates of two men who received this treatment for over one year and then had prostatectomy. There is in these slides no evidence of atrophy.

*Relation to the Pituitary Gland.*—The theories developed by Lower and his associates postulated a hyperactivity of the pituitary gland. In order to secure information on this point I have studied the pituitaries upon which the reports of Parsons and of Melechianna and Moore were based. Together these constitute 150 glands. As shown in Table I there is no difference in the weight of the pituitary gland in men with clinical benign hypertrophy, and in men without disease of the prostate of a comparable age group.

TABLE I

WEIGHT OF PITUITARY IN RELATION TO BENIGN HYPERTROPHY OF PROSTATE

TYPE OF PATIENT	NUMBER OF OBSERVATIONS	AVERAGE WEIGHT OF PITUITARY (MG.)
Men over 40 without benign hypertrophy	16	644
Men over 40 with benign hypertrophy	20	627
Women over 40	23	751

In contrast, the pituitary gland of women over the age of 40 years is considerably heavier. Histologic study for the presence of adenomas, for basophilic invasion of the posterior lobe, and for gross changes in the relative proportion of the cells reveals no relation of any of these conditions to benign hypertrophy of the prostate. The reverse relation of the state of the prostate in disease of the pituitary gland is also of interest. There are a few examples in the literature of complete destruction of the pituitary by a suprasellar cyst, producing pituitary infantilism. Histologic examination of the prostate shows complete atrophy, and in those patients who have lived to be over 40 years of age there is no evidence of benign hypertrophy. In the carefully studied cases of acromegaly reported by Cushing and Davidoff there is note of hyperplasia, but not of the formation of nodules. There are inadequate reports in the literature of patients with basophilism and of patients with Sim-

\*Professor of Urology at the University of Michigan.



monds' disease to arrive at any conclusion concerning the nature of prostatic changes.

*Urinary Excretion of Hormones.*—Although there is not entire agreement, most reports indicate that there is a slight to moderate decrease in the urinary excretion of androgens and estrogens in the urine of patients with benign hypertrophy as compared with individuals of similar age (Moore, Miller, and McLellan; Dingemanse and Laqueur). In contrast with the greatly increased excretion of prolan in the urine of postmenopausal women, there is no increase in men, either with or without benign hypertrophy (Woodman and Stimpel).

*Lipopenia.*—In most patients with benign hypertrophy there is a 30 to 40 per cent decrease in the total lipid, total cholesterol, cholesterol ester, and phospholipid in the blood. This is interpreted as evidence that the condition is a general metabolic disturbance (Boyd and Berry).

*Part of the Prostate Involved.*—The smallest and presumably the earliest lesions of benign hypertrophy of the prostate are found in the periurethral tissue cephalad to the distal end of the verumontanum. Similar small lesions are also seen about the prostatic ducts of the lateral and middle lobes, and occasionally within the lobules of the lateral lobes. Nodular hyperplasia is never observed in the posterior lobe. In pseudohermaphrodites the structure of the prostate is dependent on the sex of the gonad. If there are ovaries present, the prostate is represented only by the middle and lateral lobes; while if testes are present the entire male prostate, including the posterior lobe, surrounds the urethra (Moszkowicz). These observations indicate that the middle and lateral lobes of the prostate constitute an ambisexual organ, while the posterior lobe is a distinctly male structure. Comparison with the distribution of benign hypertrophy of the prostate further indicates that this disease involves the ambisexual part of the prostate—in other words, that part which is sensitive to both androgens and estrogens. This conclusion is further supported by a study of the prostate of the newborn infant, which is presumably exposed to excessive amounts of estrogen crossing the placenta from the blood of the mother. In the prostate of the newborn infant there is squamous metaplasia within the urethra, about the verumontanum, and in the ducts to the lateral and middle lobes (Diac; Brody and Goldman).

*Relation of the Adrenal.*—For many reasons it has been supposed that some activity of the adrenal gland is the cause or one of the causes of benign hypertrophy. It is known that the adrenal gland of the young rat is capable of maintaining the normal appearance of the prostate for as long as 40 days in both male and female animals (Price). In a qualitative study of the excretion of urinary androgens in the urine of patients with benign hypertrophy, Miller found that there is a relative increase in the amount of dehydroisoandrosterone, and a relative and absolute decrease in the amount of androsterone. Callow and Callow

and others have shown that the source of dehydroisoandrosterone in man is probably the adrenal gland; it remains after castration but disappears from the urine in diseases involving destruction of the adrenal cortex. Despite this inferential evidence of the relation of the adrenals to benign hypertrophy, no morphologic changes have been described. It is possible that more precise studies with differential staining of the androgenic cells would give a positive answer to the question. On the contrary, morphologic studies of the prostate in diseases of the adrenal gland have shown a definite relation. In the rare adrenal insufficiency of young children with hypertrophy of the adrenal glands (Dijkhuizen and Behr), there is hyperplasia of the prostate to the point where it is identical in structure with that of the adult. I have had an opportunity to study two of these cases;\* both patients died of adrenal insufficiency. At autopsy the adrenal glands were twice normal size, and the prostate showed a typical adult structure. Unfortunately, no studies for fuchsinophilic granules were made in either case. These observations do indicate, however, that the androgenic activity of the adrenal gland may be considerable. This conclusion is supported by the enlargement of the prostate in patients with a functioning tumor of the adrenal cortex. Of great interest would be studies of the female prostate in young girls with virilism and with an adrenal tumor. Despite the most assiduous search, I have not been able to find any published reports on this point. It has been shown by a number of investigators that the injection of androgenic hormones into female rats will result in great hyperplasia of the vestigial prostate in about 25 per cent of animals (Korenchevsky; Korenchevsky and Dennison; Hamilton and Wolfe). I have been able to study† the prostate in 15 cases of Addison's disease, 12 resulting from tuberculosis and 3 from primary cortical atrophy. In none did the prostate differ from the expected structure, and we must therefore conclude that the androgenic and estrogenic activity of the adrenal in adults is not of sufficient intensity to affect the structure of the prostate.

*Recurrence.*—The phenomenon of recurrence following a so-called prostatectomy is a well-recognized phenomenon. It indicates nothing more than that this operation involves removal of only the enlarged tissue, and that the basic cause of the disease remains. The average interval between the first and second operation is about 5 years, although periods as short as 2 and as long as 10 years have been reported (Kretschmer).

*Effect of the Operations of Steinach.*—According to the experimental results of Steinach, ligation and division of the vas deferens in an adult animal organism will result in hyperplasia of the interstitial cells of the testes and rejuvenation of the maleness of the organism. Under the assumption that benign hypertrophy of the prostate results from a de-

\*One at the New York Hospital under Dr. Oscar Schloss, and one at the St. Louis Children's Hospital under Dr. Alexis Hartmann.

†Through the courtesy of Dr. Shields Warren, Dr. H. G. Wells, and Dr. Douglas Symmers.

creased excretion of androgen, the Steinach II has been employed in the treatment of the disease. The results are comparable to all other methods of treatment; namely, about 50 to 60 per cent are improved (Jacobs). It is highly improbable that this improvement represents a specific effect of the ligation of the vas. Clarke has clearly shown that rest in bed, catheterization, or any other well-recognized conservative treatment will give improvement and relief of symptoms in patients with prostatic hypertrophy for periods of years.

*Relation to the Testes.*—Morphologic studies of the size and structure of the testes in patients with benign hypertrophy of the prostate have uniformly shown that there are no consistent alterations associated with this disease. Specifically there are no changes, either qualitatively or quantitatively, in the interstitial cells. The direct effect of castration on the development of disease has been discussed. The problem may, however, be approached in another way. In the medical literature there are careful pathologic reports, including microscopic description of the prostate of 28 eunuchs, eunuchoids, or individuals with pituitary infantilism who lost the secondary sexual characteristics before the age of 40 years and lived to be over 45 years of age. These include every report that could be found, and it is hoped a summary may be published soon. There is not a single example of benign hypertrophy in this group. In the population at large, similar studies would reveal that 50 per cent had evidence of nodular hyperplasia. It is highly unlikely that the absence of the condition in 28 consecutive cases of men over the age of 45 could be chance observation. We may hence conclude with statistical support that benign hypertrophy does not develop except in the presence of a functioning testis—the strongest evidence yet offered that the disease is an endocrinologic dystrophy. In fact it is positive evidence, which cannot be disputed. In patients with a teratoma of the testis in whom there is a large amount of prolan in the body fluids and in the urine, there are no consistent changes in the prostate. Certainly there is no hyperplasia. This commonly occurs in young individuals during the third decade of life, and the prostatic acini are normally lined with tall, columnar epithelium, a point overlooked by some investigators of this subject who have reported hyperplasia. In the few reports of interstitial cell tumors of the testes, hyperplasia of the prostate is noted, but it is never nodular in distribution, but rather diffuse and of the same character seen in children given large amounts of androgens.

*Metabolism of Surviving Tissue.*—Surviving slices of the tissue involved in benign hypertrophy show a type of respiration similar to that of actively growing tissue, that is, a significant Pasteur effect. Whether or not this can be interpreted as evidence that benign hypertrophy is a tumor depends on the evaluation of the entire principle of Warburg. Attempts to influence the prostate of the rabbit with hormones so that a

similar type of metabolism results have not been successful (Tolins and Moore).

*Chemistry of Prostatic Secretion.*—Differential chemical analyses of the lipids in prostatic secretion of young men and of older men with and without benign hypertrophy show no significant differences (Moore, Miller, and McLellan).

*Summary.*—The great mass of data indicates that benign hypertrophy of the prostate is an endocrinologic dystrophy. The nature of the dystrophy is not clear, but it seems certain that it is not an excessive amount of any type of hormone, but rather is a shift in the relative amounts of the various androgenic and estrogenic substances. Present evidence indicates a decreased excretion of biologically active androgen, a less striking decrease of estrogen, and a relative increase of the adrenal androgen, dehydroisoandrosterone. This, in general, means a relative estrogenic and adrenal androgenic preponderance, acting on the ambisexual part of the prostate.

#### OCCURRENCE OF BENIGN HYPERTROPHY OF THE PROSTATE IN ANIMALS

*Dogs.*—About 80 per cent of dogs over the age of 8 to 10 years show enlargement of the prostate. This is frequently referred to as benign hypertrophy, but in my opinion there is no evidence that the disease in dogs and in man are the same. Histologically, in a dog the hyperplasia is diffuse and rarely if ever occurs in the form of nodules. In the large series of canine prostates studied by Zuckerman and McKeown there was not a single example of nodular hyperplasia. Dr. William H. Feldman of the Mayo Foundation has sent me a representative group of prostates from older dogs, used in the study of Schlotthauer. In none of these were there nodules. It is possible that the etiologic factors are the same in man and in the dog, but the response on the part of the tissues is different—in the dog, diffuse hyperplasia, and in man, nodular hyperplasia. The general structure of the canine prostate is similar to that of man, and aside from monkeys this species seems the best experimental animal for investigation.

*Monkeys.*—So far as I am aware there are no reports of nodular hyperplasia of the prostate in older monkeys, but this means little. Most monkeys employed in the laboratory are less than 3 years old, and have not yet gone through puberty. It is to be hoped that the colony in Puerto Rico will furnish a number of older monkeys, comparable in age to the man of 60 or 70 years of age. Until these studies are carried out, no statement concerning the natural incidence of prostatic disease in the monkey can be made.

*Rat.*—The rat has served for most of the experimental studies on the sex hormones. There is a single case report by Deming, Jenkins, and van Wagenen of a nodular type of hyperplasia in the suburethral tissues of the rat. The appearance shown in their published photomicrographs is not similar to that of the human disease.

*Other Species.*—In one lemur, Fox reported a papillary adenoma of the prostate. H. N. S. Green (personal communication) states that he has seen one typical nodular hyperplasia of the prostate in a rabbit, but both the tissues and the record were lost, unfortunately.

#### EXPERIMENTAL PRODUCTION OF BENIGN HYPERTROPHY OF THE PROSTATE

There are no convincing reports in the medical literature that a condition identical or even similar to benign hypertrophy has been produced in experimental animals. The injection of androgens leads to diffuse hyperplasia. The injection of estrogens leads to metaplasia and some hyperplasia of tissues about the urethra. In neither are nodules formed of either stroma or epithelium. These results indicate that the problem is far more complex than the simple injection of excessive amounts of one hormone. Our own experiments have been directed toward the implantation of pellets of various hormones into castrated animals, in an attempt to reproduce approximately the hormonal status of men with the disease. This involves injection of androgen at a submaintenance level, the injection of sufficient estrogen to be just in excess, and the injection of dehydroisoandrosterone in amounts from 5 to 10 times that of the active androgen. The results have so far been negative. We have also attempted to bring about nodular hyperplasia by periodic injections in castrated rats. Adult animals were given 1 mg. once every 10 days for periods up to 180 days. In 3 there was suggestive encapsulation of lobules of the prostate, but not sufficiently clear to claim reproduction of the disease.

#### EVIDENCE THAT CARCINOMA OF THE PROSTATE IS AN ENDOCRINOLOGIC DYSTROPHY

*Age Incidence.*—Carcinoma of the prostate is a distinctive tumor in that it is definitely a neoplasm of increasing age. There are not over 25 cases in the world literature of carcinoma of the prostate in individuals less than 30 years of age (Joeck). It has been established that after the age of 40 years there is a gradual decrease in the urinary androgens which are biochemically active. As the urinary androgens decrease there is a progressive increase in the incidence of carcinoma of the prostate, until during the eighth decade it is one of the most important and frequent of all carcinomas (Duff).

*Racial Incidence.*—Although racial incidence does not prove that a tumor is related to hormones, it does demonstrate a constitutional or genetic factor which may in turn control the endocrine status. In Chinese people, carcinoma of the prostate is a rare form of tumor, and in the series studied by Hu and Ch'in there was only one instance of carcinoma of the prostate in 379 carcinomas in Chinese men.

*Incidence in Eunuchs and Eunuchoids.*—To my knowledge there is not a single instance in the literature of the occurrence of carcinoma of

the prostate in a eunuch nor in a true eunuchoid. The criteria for the eunuchoid state are the changes in the secondary sexual organs, and not the fact that the testes are small. It has been repeatedly demonstrated that there is no correlation between the size of the testes and the strength of the secondary sexual characteristics nor the excretion of urinary androgens.

*Effect of Irradiation of the Testes.*—Irradiation of the testes leads to marked atrophy of the seminiferous tubules, and to slight atrophy of the interstitial cells. There is an associated decrease in urinary androgens. According to the report of Munger, patients with carcinoma of the prostate given 500 R. of irradiation by high voltage x-ray to each testis did better and survived in a higher percentage than the patients treated only by resection. There is not, however, the striking effect observed after castration, and irradiation of the testes cannot be recommended as an alternate therapeutic procedure at the present time.

*The Effect of Castration.*—This topic is completely covered by Dr. Charles Huggins in another article of this symposium, and will not be discussed here.

*Effects of Estrogens.*—By serial biopsy, Schenken and Burns demonstrated that the administration of stilbestrol over periods up to 60 days brought about profound degenerative changes in the neoplastic cells of carcinoma of the prostate.

*Effects of Androgens.*—At the time of this communication there are no histologic studies to demonstrate the effect of androgens on carcinoma of the prostate, but in 3 cases reported by Huggins, Stevens, and Hodges there was an increase of pain in the legs and an increase of the serum acid phosphatase following the administration of testosterone propionate. In one case studied by Moore and McLellan an individual with carcinoma of the prostate was given 600 mg. of testosterone propionate over a period of 12 days. The histologic appearance of this carcinoma was not significantly different from the usual carcinoma of the prostate. The man died with multiple metastases 12 months after a radical perineal prostatectomy.

*Acid Phosphatase.*—An acid phosphatase most active at a pH of 5 is present in prostatic tissue in small amounts during infancy and childhood, and in large amounts after puberty (Moore and Hanzel; Gutman and Gutman). This observation clearly indicates that secretory activity and adulthood in man are directly related to the amount of acid phosphatase in the prostate. Experimental support is given by the demonstration that the low prepuberal levels in the monkey may be promptly increased by injections of testosterone propionate (Gutman and Gutman). In patients with carcinoma of the prostate and metastases to bone there is a remarkable increase in the acid phosphatase of the serum (Gutman and Gutman; Robinson, Gutman, and Gutman; Barringer and Woodard). Castration or injection of estrogens will cause a decrease in

the serum acid phosphatase, while injection of androgens results in a further increase (Huggins and Hodges). The excessive phosphatase is readily demonstrable in histologic sections of the neoplastic tissue (Huggins, Stevens, and Hodges).

#### OCCURRENCE OF CARCINOMA OF THE PROSTATE IN ANIMALS

In sharp contrast with the situation in man, carcinoma of the prostate is apparently rare in all animals except the dog. This rarity may be only apparent, because most of the animals that have been studied are domesticated by man and are sacrificed as a source of food during what amounts to childhood. Wild animals brought into captivity in most instances do not live a full lifetime.

*Primates.*—Of all of the monkeys, chimpanzees, and other primates studied in the laboratory during the past 100 years, there is only a single observation of a primary carcinoma of the prostate. This was noted in an old monkey (*Rhesus mulatta*) of unknown age, by Engle and Stout.

*Dogs.*—Many dogs live for over 10 or 12 years, yet there are relatively few observations on carcinomas of the prostate. Sticker collected the autopsy material on dogs from Berlin Veterinary Institute and the Dresden Veterinary Institute. In Berlin there were 1,306 autopsies on dogs, with 72 tumors, of which 11 were primary in the prostate. The youngest of these 11 dogs was between 6 and 8 years of age. Of 111 tumors in dogs observed at the Dresden Institute none were primary in the prostate. In a summary of his own observations and those recorded in the literature, Sticker noted 11 carcinomas of the prostate among 956 carcinomas of dogs. Krause observed a carcinoma of the prostate or urethra in a cryptorchid dog. Folger, in a review of tumors in animals in 1917, could find only 5 reports in the European literature of carcinoma of the prostate in dogs. They were all adenocarcinomas. Feldman, in his survey of neoplasms in domesticated animals in 1932, gave no added examples of citations from the literature. In their critical study of the prostate in 243 dogs of all ages, Zuckerman and McKeown found one carcinoma of the prostate in a dog with an adenocarcinoma of the testis. It is their opinion that this association was probably fortuitous. Of 15 dogs with adenocarcinomas of the testes, the prostate in 5 showed advanced squamous metaplasia of the glandular system, an indication of powerful estrogenic stimulation. In this series of 243 dogs, 89 were estimated to be 6 years of age or older. In view of the high incidence of latent carcinoma of the prostate in man (Moore; Rich), 15 to 20 per cent, it is significant that no latent carcinoma of the prostate was found in these older dogs.

*Other Species.*—Sticker observed 110 tumors in bovines, with 1 carcinoma of the prostate. Among 509 tumors in horses, again there was only 1 carcinoma of the prostate. McCoy examined about 100,000 wild rats and found 103 primary tumors, none of which originated in the

prostate. Sticker observed no carcinoma of the prostate among 21 carcinomas in the cat. Among the many reports by Slye and her co-workers there is no mention of carcinoma of the prostate. One sarcoma of the seminal vesicle in a mouse was observed. In connection with the experimental production of so-called squamous-cell carcinoma of the prostate with estrogens, it is significant that of 153 nonexperimental squamous-cell carcinomas in mice, none was primary in the prostate (Slye, Holmes, and Wells). Among 94 tumors of captive wild animals Fox reported no carcinoma of the prostate, but one papillary adenoma in a ring-tailed lemur (*Lemur catta*). So far as I am aware no carcinoma of the prostate in the rabbit or in the guinea pig has been recorded.

#### EXPERIMENTAL PRODUCTION OF CARCINOMA OF THE PROSTATE IN ANIMALS

*By Injection of Androgens.*—In spite of the evidence in man that carcinoma of the prostate is improved by orchidectomy, and made worse by the injection of androgens, there are no reports of the production of carcinoma of the prostate in animals by injection of androgens. These studies include those of Rössle and Zahler on adult dogs and of Zahler on senile dogs. In both instances the period of study was relatively short, and the amount of androgen given was probably inadequate. Zuckerman and Parkes injected 242.5 mg. of testosterone propionate into a castrated rhesus monkey during 91 days. The histologic structure of the prostate was normal. In lemurs, up to 1,985 mg. in 157 days gave only diffuse hypertrophy and hyperplasia (Zuckerman and Sandys).

*By Injection of Estrogens.*—Lacassagne, Lacassagne and Villela, and Burrows and Kennaway independently observed that long-continued administration of estrogen brought about pronounced squamous metaplasia of the epithelium of the prostate of the mouse. This has frequently been referred to as a squamous-cell carcinoma, but there is no evidence that the cells take on neoplastic potentialities. From my own experience, based on observations on 6 mice and 3 rats given 250 international units of estradiol benzoate weekly for 173 days, there was nothing more than metaplasia. The basement membrane was sharp and there was no invasion of the surrounding stroma by epithelial cells. A similar change occurs in the rhesus monkey, and here the greatest degree of hyperplasia of cells and metaplasia of epithelium is in the utricular bed (Zuckerman). Two Hanuman lemurs given 287.2 and 121.5 mg. of estrone for 483 and 316 days, respectively, showed no evidence of carcinoma. There was only excessive epithelial hyperplasia in the prostatic utricle and in the prostatic ducts (Zuckerman and Sandys). In rabbits administration of estrogens for short periods of time bring about squamous metaplasia of the urethra about the orifice of the seminal vesicles, and migration of polymorphonuclear leucocytes in large numbers through the metaplastic epithelium.



*By the Use of Carcinogenic Chemicals.*—Carcinoma of the prostate does not result from the application of carcinogenic chemicals onto the skin, or injection into the subcutaneous tissues. Moore and Melchionna have studied the effect of benzpyrene dissolved in lard injected directly into the prostate of the white rat. After 110 days, tumors were found in the prostate, and previous castration had no appreciable effect on the time of appearance or incidence of tumors. Both squamous-cell carcinoma and leiomyosarcoma were observed. In animals over 500 days of age and in animals injected with testosterone propionate the incidence of tumors was somewhat higher, but the experiments did not encompass a sufficient number of animals to justify definite conclusions. The whole problem of the relation of hormones to experimental carcinoma in the white rat is now under investigation in this laboratory.

#### SUMMARY

1. There is inferential evidence but no definitive proof that benign hypertrophy and carcinoma of the prostate are in part caused by an imbalance of the endocrinologic status of the patient.

2. Benign hypertrophy of the prostate is apparently a distinctive disease of man. An exactly analogous lesion has not been observed in animals, but observations on animals of comparable age are limited in number.

3. Carcinoma of the prostate occurs in dogs and rarely in other species. Occult carcinoma of the prostate, a common lesion in older men, has not been observed in animals, in spite of investigation of suitable specimens.

4. Benign hypertrophy of the prostate has not been produced in experimental animals.

5. An adenocarcinoma of the prostate similar to that in man has not been produced in experimental animals. The injection of the carcinogen, benzpyrene, results in the formation of squamous-cell carcinoma and sarcoma.

#### REFERENCES

- Barringer, B. S., and Woodard, H. Q.: Prostatic Carcinoma With Extensive Intraprostatic Calcification, *Tr. Am. A. Genito-Urin. Surgeons* 31: 363-369, 1938.
- Boyd, E. M., and Berry, N. E.: Prostatic Hypertrophy as Part of a Generalized Metabolic Disease. Evidence of the Presence of a Lipopenia, *J. Urol.* 41: 406-411, 1939.
- Brody, H., and Goldman, S.: Metaplasia of the Epithelium of the Prostatic Glands, Utricle and Urethra of the Fetus and Newborn Infant, *Arch. Path.* 29: 494-504, 1940.
- Burrows, H., and Kennaway, N. M.: On Some Effects Produced by Applying Oestrin to the Skin of Mice, *Am. J. Cancer* 20: 48-57, 1934.
- Callow, N. H., and Callow, R. K.: Excretion of Androgens by Eunuchs: The Isolation of 17-ketosteroids From the Urine, *Biochem. J.* 34: 276-279, 1940.
- Chang, H. L., and Char, G. Y.: Benign Hypertrophy of the Prostate, *Chinese M. J.* 50: 1707-1722, 1936.
- Clarke, R.: The Prostate and the Endocrines, *Brit. J. Urol.* 9: 254-271, 1937.
- Cushing, H., and Davidoff, L. M.: The Pathological Findings in Four Autopsied Cases of Acromegaly With a Discussion of Their Significance, Monograph No. 22, New York, 1927, Rockefeller Institute for Medical Research.

- D'Aunoy, R., Schenken, J. R., and Burns, E. L.: The Relative Incidence of Hyperplasia of the Prostate in the White and Colored Races in Louisiana, South. M. J. 32: 47-52, 1939.
- Deming, C. L., Jenkins, R. H., and van Wagenen, G.: Some Endocrinological Relationships of Prostatic Hypertrophy. Clinical and Experimental Studies; Preliminary Report, J. Urol. 33: 388-399, 1935.
- Deming, C. L., Jenkins, R. H., and van Wagenen, G.: Further Studies in Endocrinologic Relationships of Prostatic Hypertrophy; Effect of Castration on Suburethral Glands in Posterior Urethra of Rat, J. Urol. 34: 678-685, 1935.
- Derbes, V. de P., Leche, S. M., and Hooker, C. W.: The Incidence of Benign Prostatic Hypertrophy Among the Whites and Negroes in New Orleans, J. Urol. 38: 383-388, 1937.
- Dinea, C.: Anatomische und experimentelle Untersuchungen zur Pathogenese der histologischen Veränderungen der Prostata bei Neugeborenen und Kindern vor der Pubertät. Virchows Arch. f. path. Anat. 306: 1-24, 1940.
- Dijkhuizen, R. K., and Behr, E.: Adrenal Hypertrophy in Infants. A New Clinical Entity of the Neonatal Period, Acta paediat. 27: (Supplement) 279-295, 1939-40.
- Dingemans, E., and Laqueur, E.: The Content of Male and Female Hormone in the Urine of Patients With Prostatic Hypertrophy, J. Urol. 44: 530-540, 1940.
- Draper, G.: Human Constitution, New York, 1924, W. B. Saunders Company.
- Draper, J. W., Slaughter, G., and Denslow, C.: The Effect of Testosterone Propionate on Benign Prostatic Hypertrophy, J. Urol. 45: 539-547, 1941.
- Duff, J.: Cancer Mortality, Bladder, Kidney, Prostate, 1917 to 1928, J. Urol. 32: 346-353, 1934.
- Engle, E. T., and Stout, A. P.: Spontaneous Primary Carcinoma of the Prostate in a Monkey (*Macaca mulatta*). Am. J. Cancer 39: 334-337, 1940.
- Feldman, W. H.: Neoplasms of Domesticated Animals. Mayo Clinic Monographs, Philadelphia, 1932, W. B. Saunders Company.
- Folger, A. F.: Geschwulste bei Tieren, Ergebn. d. allg. Path. u. path. Anat. 18: 372-676, 1917.
- Fox, H.: Disease in Captive Wild Mammals and Birds. Incidence, Description, Comparison, Philadelphia, 1923, J. B. Lippincott Company.
- Gover, M.: A Statistical Study of the Etiology of Benign Hypertrophy of the Prostate Gland, Johns Hopkins Hosp. Rep. 21: 231-295, 1923.
- Gutman, A. B., and Gutman, E. B.: "Acid" Phosphatase and Functional Activity of the Prostate (Man) and Preputial Glands (Rats), Proc. Soc. Exper. Biol. & Med. 39: 529-532, 1938.
- Gutman, A. B., and Gutman, E. B.: An "Acid" Phosphatase Occurring in the Serum of Patients With Metastasizing Carcinoma of the Prostate Gland, J. Clin. Investigation 17: 473-478, 1938.
- Gutman, A. B., and Gutman, E. B.: Adult Phosphatase Levels in Prepubertal Rhesus Prostate Tissue After Testosterone Propionate, Proc. Soc. Exper. Biol. & Med. 41: 277-281, 1939.
- Hamilton, J. B., and Wolfe, J. M.: Prostatic Type of Paraurethral Glands Induced in Female Rats by Administration of Male Sex Hormone, Proc. Soc. Exper. Biol. & Med. 36: 465-468, 1937.
- Heckel, N. J.: The Influence of Testosterone-Propionate Upon Benign Prostatic Hypertrophy and Spermatogenesis: A Clinical and Pathological Study in the Human, J. Urol. 43: 286-308, 1940.
- Hu, C. H., and Ch'ın, K. Y.: A Statistical Study of 2,179 Tumors Occurring in the Chinese, Chinese M. J. (Supplement) 1: 43-63, 1936.
- Huggins, C., and Hodges, C. V.: Studies on Prostatic Cancer: I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate, Cancer Research 1: 293-297, 1941.
- Huggins, C., and Stevens, R. A.: The Effect of Castration on Benign Hypertrophy of the Prostate in Man, J. Urol. 43: 705-714, 1940.
- Huggins, C., Stevens, R. E., Jr., and Hodges, C. V.: Studies on Prostatic Cancer. II. The Effects of Castration on Advanced Carcinoma of the Prostate Gland, Arch. Surg. 43: 209-223, 1941.
- Jacobs, A.: A Critical Review of the Steinach II Operation as a Method of Treating Prostatic Obstruction, Glasgow M. J. 131: 166-170, 1939.
- Joeck, H.: Ueber die Häufigkeit, Altersverteilung und das Auftreten des Prostatacarcinoma in jugendlichen Alter, Arch. f. klin. Chir. 197: 885-896, 1939-40.
- Kaufmann, O.: Konkordantes Vorkommen von Prostatahypertrophie bei einem eineiigen Zwillingsspaar, Med. Klin. 34: 580-681, 1938.

- Keller, W. F., and Hull, W. M.: Histopathological Changes in the Prostate Following Testosterone Propionate Therapy, *Urol. & Cutan. Rev.* 44: 18-23, 1940.
- Korenchevsky, V.: The Female Prostatic Gland and Its Reaction to Male Sexual Compounds, *J. Physiol.* 90: 371-376, 1937.
- Korenchevsky, V., and Dennison, M.: Histology of Sex Organs of Ovariectomized Rats Treated With Male or Female Sex Hormones Alone or With Both Simultaneously, *J. Path. & Bact.* 42: 91-104, 1936.
- Krause, C.: Beitrag zum Prostatakrebs und Kryptorchismus des Hundes, *Frankfurt. Ztschr. f. Path.* 41: 405-422, 1931.
- Kretschmer, H. L.: Recurrence Following Suprapubic Prostatectomy for Benign Hypertrophy, *Surg., Gynec. & Obst.* 53: 829-831, 1931.
- Lacassagne, A.: Métaplasie épidermoïde de la prostate provoquée chez la souris, par des injections répétées de fortes doses de folliculine, *Compt. rend. Soc. de biol.* 113: 590-592, 1933.
- Lacassagne, A., and Villela, E.: Processus histologique de la métaplasie épidermoïde des lobes prostatiques postérieurs, chez la souris male folliculinée, *Compt. rend. Soc. de biol.* 114: 870-873, 1933.
- Lower, W. E., Engel, W. J., and McCullagh, D. R.: Summary of Experimental Research on Control of Benign Hypertrophy and Preliminary Clinical Report, *J. Urol.* 34: 670-677, 1935.
- McCoy, G. W.: A Preliminary Report on Tumors Found in Wild Rats, *J. M. Research* 16: 285-296, 1909.
- Melchionna, R. H., and Moore, R. A.: The Pharyngeal Pituitary Gland, *Am. J. Path.* 14: 763-771, 1938.
- Miller, M. L.: The Neutral Steroids in the Urine of Individuals With Benign Hypertrophy of the Prostate, *J. Urol.* (In press.)
- Moore, R. A.: The Morphology of Small Prostatic Carcinoma, *J. Urol.* 33: 224-234, 1935.
- Moore, R. A., and Hanzel, R. F.: Chemical Composition of Prostatic Corpora Amylacea and Calculi, *Arch. Path.* 22: 41-54, 1936.
- Moore, R. A., and McLellan, A. M.: A Histological Study of the Effect of the Sex Hormones on the Human Prostate, *J. Urol.* 40: 641-657, 1938.
- Moore, R. A., and Melchionna, R. H.: Production of Tumors of the Prostate of the White Rat With 1:2-benzpyrene, *Am. J. Cancer* 30: 731-741, 1937.
- Moore, R. A., Miller, M. L., and McLellan, A.: The Urinary Excretion of Androgens by Patients With Benign Hypertrophy of the Prostate, *J. Urol.* 44: 727-737, 1940.
- Moore, R. A., Miller, M. L., and McLellan, A.: The Chemical Composition of Prostatic Secretion in Relation to Benign Hypertrophy of the Prostate, *J. Urol.* 46: 132-137, 1941.
- Moszkowicz, L.: Die Prostata der Zwitter und die Systematik des Zwittertums, *Virchows Arch. f. path. Anat.* 295: 211-235, 1935.
- Moszkowicz, L.: Biologische Grundlagen zum Problem des männlichen Klimakterium, *Wien. klin. Wchnschr.* 50: 1443-1448, 1937.
- Munger, A. D.: Experiences in the Treatment of Carcinoma of the Prostate With Irradiation of the Testicles, *J. Urol.* 46: 1007-1011, 1941.
- Nancrede, C. B.: Discussion of paper by Cabot, A. T.: The Question of Castration for Enlarged Prostate, *Tr. Am. S. A.* 14: 189-238, 1896.
- Parsons, R. J.: The Pituitary Gland and Its Relation to Age, Hypertension and Pathological Processes: A Study of 107 Unselected Pituitaries. Medical Papers, Christian Birthday Volume, February, 1936.
- Price, D.: Normal Development and Regression of the Prostate Gland of the Female Rat, *Proc. Soc. Exper. Biol. & Med.* 41: 580-583, 1939.
- Rich, A. R.: On the Frequency of Occurrence of Orcult Carcinoma of the Prostate, *J. Urol.* 33: 215-223, 1935.
- Robinson, J. N., Gutman, E. B., and Gutman, A. B.: Clinical Significance of Increased Serum "Acid" Phosphatase in Patients With Bone Metastases Secondary to Prostatic Carcinoma, *J. Urol.* 42: 602-617, 1939.
- Rüssle, R., and Zahler, H.: Experimentelle Untersuchungen über Hoden- und Prostataveränderungen durch Zufuhr von Hodenwirkstoffen, *Virchows Arch. f. path. Anat.* 302: 251-300, 1938.
- Schenken, J. R., and Burns, E. L.: The Cytologic Changes in Carcinoma of the Human Prostate Gland Following Administration of Diethylstilbestrol Dipropionate, Presented at 42nd Annual Meeting of the American Association of Pathology and Bacteriology, 1942.
- Schlotthauer, C. F.: Observations on the Prostate Gland of the Dog, *J. Am. Vet. M. A.* 81: 645-650, 1932.

- Slye, M., Holmes, H. F., and Wells, H. G.: Primary Spontaneous Tumors of the Testicle and Seminal Vesicle in Mice and Other Animals. XII. Studies in the Incidence and Inheritability of Spontaneous Tumors in Mice, *J. Cancer Research* 4: 207-228, 1919.
- Slye, M., Holmes, H. F., and Wells, H. G.: The Occurrence of Squamous-Cell Carcinoma in Mice, *J. Cancer Research* 6: 180-182, 1921.
- Sticker, A.: Ueber den Krebs der Thiere insbesondere über die Empfänglichkeit der verschiedenen Hausthierarten und über die Unterschiede des Thier und Menschenkrebses, *Arch. f. klin. Chir.* 65: 616-696, 1902.
- Stimpel, A.: Über die Prodnauausscheidung beim alten Manne, insbesondere beim Prostater, *Klin. Wchnschr.* 19: 597-598, 1910.
- Sutton, M. R.: Creatine-Creatinine Metabolism in Older Patients With Benign Prostatic Enlargement, *J. Clin. Endocrinol.* 1: 882-888, 1911.
- Tolins, S., and Moore, R. A.: The Metabolism of Surviving Prostatic Tissue in Relation to Benign Hypertrophy of the Prostate, *J. Urol.* 46: 138-142, 1941.
- White, J. W.: The Results of Double Castration in Hypertrophy of the Prostate, *Ann. Surg.* 22: 1-80, 1895.
- Woodman, D.: Output of Prolan A in Urine in Certain Extragenital Conditions. Report of an Investigation, *Brit. M. J.* 1: 666-668, 1938.
- Young, H. H.: The Treatment of Prostatic Hypertrophy by Conservative Perineal Prostatectomy. An Analysis of Cases and Results Based on a Detailed Report of 115 Cases, *Johns Hopkins Hosp. Rep.* 11: 1-176, 1906.
- Zahler, H.: Die Auffrischung greisenhafter Hunde mittels Hodenwirkstoffen und ihre Auswirkung auf Hoden und Prostata, *Virchows Arch. f. path. Anat.* 305: 65-107, 1939.
- Zuckerman, S.: The Effects of Prolonged Oestrogenic Stimulation on the Prostate of the Rhesus Monkey, *J. Anat.* 72: 261-276, 1938.
- Zuckerman, S., and McKeown, T.: The Canine Prostate in Relation to Normal and Abnormal Testicular Changes, *J. Path. & Bact.* 46: 7-19, 1938.
- Zuckerman, S., and Parkes, A. S.: The Effects of Male Hormone on a Mature Castrated Rhesus Monkey, *J. Anat.* 72: 277-279, 1938.
- Zuckerman, S., and Sandys, O. C.: Further Observations on the Effects of Sex Hormones on the Prostate and Seminal Vesicles of Monkeys, *J. Anat.* 73: 597-616, 1939.

## Book Review

---

**The Modern Management of Colitis.** By Jacob A. Bargen, M.D., Chief of the Section on Intestinal Diseases, Mayo Clinic, Rochester, Minn. Ed. 1. Pp. 322, with 148 illustrations. Springfield, Ill., 1943. Charles C Thomas, Publisher. \$7.

The author of this book is well known for his work on ulcerative colitis. This volume is essentially an attempt to summarize the author's broad experience in that field. Whereas other conditions, such as the irritable colon, allergic colitis, "deficiency colitis," regional colitis, lymphogranuloma venereum, tuberculosis, and amebic colitis, are all dealt with in a brief manner, it is with the many manifestations of so-called chronic ulcerative colitis that the author is especially concerned in this treatise. Bargen recognizes the following types of chronic ulcerative colitis:

1. Thrombo-ulcerative colitis of streptococcal origin, constituting approximately one-half of all observed varieties of all types of colitis. The entire colon is involved.

2. The regional or segmental type with rectum uninvolved, the most favorable type in that surgical excision may be performed.

3. A type which the author designates "chronic ulcerative colitis"—a division about which the author probably is somewhat confused, for in attempting to characterize it, he says, in part, concerning its proctoscopic appearance: "The gross appearance of the interior of the bowel may be considered 'typical' because of its 'atypical appearance.'"

The author regards Type I, thrombo-ulcerative colitis, as being primarily a medical disease and employs ileostomy only as a last resort in these cases—a conclusion which he appears able to justify by an analysis of the Mayo Clinic experience. The author regards ileostomy as inevitable in Type III. There are a large number of cases cited depicting the various types of disease described. The illustrations (largely roentgenograms, are satisfactory and a list of eighty-five references is appended. The monograph may be recommended enthusiastically as summarizing the author's rich experience in a chapter of medicine that is not particularly bright and in which more illumination and enlightenment are needed.

# SURGERY

Vol. 16

AUGUST, 1944

No. 2

## Original Communications

### *Symposium on Endocrinology of Neoplastic Diseases*

*(Concluded)*

#### THE ENDOCRINE TREATMENT OF CANCERS OF THE PROSTATE GLAND

ARCHIE L. DEAN, M.D., HELEN Q. WOODARD, PH.D., AND  
GRAY H. TWOMBLY, M.D., NEW YORK, N. Y.

*(From the Departments of Urology, Biochemistry, and Endocrinology,  
Memorial Hospital)*

ASSOCIATION between the function of the testes and the prostate has been recognized for many years. Harvey observed that when the hedgehog hibernates the testes atrophy and the prostate also becomes smaller. He observed also that the prostates of bulls became smaller after castration. In 1893, White, on the basis of animal experiments, stated that the castration of dogs "was followed invariably and promptly by atrophy, first of glandular and then of muscular elements, of the prostate." Two years later the same worker reported the generally favorable clinical results in a group of 111 patients castrated by him and others because of prostatic enlargement. In 1898, results were reported following the castration of a number of women for cancer of the breast. Although this treatment of breast cancer never proved successful, it did stimulate further treatment of prostatic tumors by modification of the endocrines.

After a few years the treatment of prostatic enlargement by castration was largely abandoned. This was probably due to a number of factors. The majority of patients who visited physicians with bladder neck obstruction perhaps required relief more promptly than could be brought about by removal of the testes; careful pathologic differentiation between benign and malignant enlargements of the gland were not performed routinely; and finally, at this time there was greatly increased

interest in the development of surgical methods for the relief of prostatic enlargement. For these reasons, and perhaps others, it was years before further attempts were made to treat prostatic tumors by endocrine methods. Beginning in 1934, Randall castrated five men who had prostate cancers. Since it was necessary to relieve obstruction of the bladder neck in each of these patients, transurethral resections were performed as well. Each of these patients followed a course which appeared to Randall to be what one would expect after transurethral resection alone. Therefore, the work was not reported until 1942. At about the time Randall's work was performed, or a little later, Munger irradiated the testes of a number of men with prostatic cancers. He noted that these patients did better than his other patients treated by different methods. A number of competent urologists examined Munger's patients rectally and could find no evidence of prostatic carcinoma. Beginning about 1938, a number of investigators began to treat patients with prostatic carcinomas with female sex hormones.

The development of the chemical tests, which show so accurately the condition of the patient with prostatic carcinoma that his response to treatment can be followed closely, is another phase of our subject. In 1935 Kutscher and Wolbergs isolated from the prostate a phosphatase which had its maximal activity in an acid solution. In 1936 the Gutmans and Sproul discovered that bones, the site of metastases from carcinoma of the prostate, contained this acid phosphatase in addition to the usual and well-known alkaline bone phosphatase. In 1938 the Gutmans established the fact that there was but little acid phosphatase in the prostates of infants and that this substance increased greatly with puberty. These workers found acid phosphatase in the normal adult prostate, the hyperplastic prostate, and the cancerous prostate. More recently, Gomori, through his microphosphatase tests, demonstrated that acid phosphatase was present only in the adult epithelial cells of the gland. This was the first demonstration of a chemical secondary sex characteristic.

After this pioneer work, assays of the serum acid and alkaline phosphatases came into general clinical use, and their accuracy in diagnosing cancers of the prostate and estimating the extent of the disease has been proved. More specifically, on the basis of the phosphatase findings, four groups of patients have been recognized:

1. Normal men in whom there is no increase in either the serum acid or alkaline phosphatases. It is noteworthy that since every adult prostate contains large quantities of acid phosphatase and that the serum acid phosphatase of men is the same as that of women, who have no organ rich in acid phosphatase, this substance is prevented from entering the circulation by an intact prostatic capsule.

2. Patients with cancers of the prostate and normal amounts of serum acid and alkaline phosphatase. In this small but definite group one may

operate with an excellent chance of removing all of the disease because the tumor probably has not grown beyond the gland.

3. A group consisting of the great majority of patients with prostatic carcinoma. The tumor has grown through the gland capsule and there may or may not be distant metastases. In our experience 73 per cent of these patients show increased serum acid phosphatase.

4. Patients with prostatic cancers which metastasize to bones. There is nearly always an increase in the serum alkaline phosphatase in these cases. The quantity of this substance in the serum so accurately represents the amount of reaction of the bones to the invasion of prostatic carcinoma that quantitative assays give clinical information not obtained by any other tests, such as the roentgen rays.

From the clinical standpoint, cancers of the prostate have long been considered incurable. The frequency of the disease was well recognized and it had been closely studied by many investigators. Radical operations had been devised for removing all of the affected prostate gland with adjacent structures; external radiation from the most efficient sources had been used in many cases, and interstitial radiation had been employed frequently, with radon seeds implanted both through perineal and suprapubic approaches. In spite of the most careful use of these forms of treatment, the clinical results seldom showed more than various degrees of palliation. It was against this background of deserved pessimism that the announcement of Huggins and his co-workers stood out in marked contrast. This investigator reported that after the relatively insignificant operation of castration, patients with advanced prostatic cancers improved in general, their primary tumors became smaller, and metastases regressed.

Huggins' clinical work was based on a long series of ingenious animal experiments. Dogs' prostates were isolated from their bladders and a study was made of the normal excretion of prostatic fluid. It was then demonstrated that the administration of androgens stimulated prostatic activity and increased the flow of prostatic fluid. It was shown also that the administration of estrogens promptly stopped the production of prostatic fluid. It was learned that the administration of androgens caused hyperplasia of the epithelial cells of the prostate and that, in some cases, metaplasia became so marked that the appearance of the gland simulated cancer. When estrogens were given, these glands promptly returned to normal. Huggins also showed that after surgical castration prostatic secretion stopped and metaplasia of the epithelial cells regressed.

As soon as this work was reported we began the endocrine treatment of patients with prostatic cancers and treated each case like any complex clinical research problem. We have attempted to give our patients every benefit from modification of the endocrines, and at the same time we have attempted to learn the factors which bring about the clinical changes and the nature of these changes. We have, therefore, stud-



ied carefully each patient from the clinical, chemical, and endocrinologic viewpoint. In addition to frequent clinical and roentgenologic examinations before and after treatment, at short intervals routine assays have been made of the acid and alkaline phosphatases, phosphorus, calcium, and chlorides of the blood, and of the creatinin, androgens, estrogens, and gonadotropic hormones excreted in the urine. Our clinical experience with the endocrine treatment of prostatic cancers is based on approximately 100 cases. Of these, about 40 have been observed for only short periods, or have been lost to follow-up. Sixty patients have been observed for six months or more or have died within six months after they were first seen. Thirty-one were treated by surgical castration and twenty-nine by stilbestrol. As these groups are small, statistical studies would be misleading and will not be attempted.

In our experience, surgical castration almost invariably has given prompt relief to patients with prostatic cancer. The improvement of patients with hopelessly far advanced disease is one of the most spectacular changes to be observed in clinical medicine. In no case did we withhold orchiectomy because of advanced disease, although many patients seemed near death at the time of operation. In a number of instances, patients had been confined to bed for months because of pain due to metastases. Frequently they had acquired serious contractures of their lower limbs. It was surprising, but not at all unusual, to see these individuals learning to walk within a few days of operation. Almost without exception, pain disappeared within forty-eight hours. In the majority of cases it had almost gone within twenty-four hours. Appetites became remarkably good, body weight increased rapidly, strength returned, and a large proportion of the men resumed their former occupations and could engage actively in sports. Regression in the size of metastases to soft parts was prompt. Large suprapubic masses, proved cancerous by biopsy, completely disappeared within two weeks of castration. Similarly, metastases in lymph nodes could no longer be felt from two to three weeks after operation. In a number of instances, metastases in the lungs could no longer be demonstrated a short time after treatment. After orchiectomy we were able to show diminution in the size of the primary prostatic tumor only occasionally, and we usually failed to observe a decrease in the amount of residual urine. Roentgenograms of the skeleton were made at trimonthly intervals, but changes in the roentgenographic appearance of the bones were difficult to interpret. The usual metastasis in bone from a prostatic carcinoma is shown as an area of increased bone density. As the patient improved and healing took place in the bone, one would expect a still further degree of bone density to be produced. We feel that we have not had sufficient experience in observing these changes to recognize the clinical status of bone lesions accurately by their roentgenographic appearance. On the other hand, we have seen patients, apparently greatly benefited by castration, in whom bone metastases seemed to be spread-

ing. We also observed what appeared to be improvement in a metastatic area on the right side of a pelvis, while at the same time, an obvious metastasis appeared and grew larger in the left pelvic bones of the same patient. We believe that in a certain proportion of patients bone metastases improved substantially, but just how frequently this occurs we are unable at present to state.

After a varying period of apparently good health, which, on the average lasted eight months, the majority of our castrated patients relapsed. Usually the relapse was first suspected because pains recurred. Phosphatase assays also indicated a relapse at about the same time that it was apparent to clinical observation.

While the great majority of castrated patients improved, a certain small percentage continued an uninterrupted downhill course and died a short time after operation.

Histologic studies of the testes removed from our patients, in practically all cases, showed moderate tubular atrophy with from slight to marked interstitial cell hyperplasia. All of the testes we removed appeared grossly within normal limits.

After observing so many relapses following castration, we began to treat a larger proportion of our patients with stilbestrol, administered by mouth. Although this drug sometimes causes nausea and vomiting, our patients had little difficulty if 1 mg. was taken daily at bedtime. While the improvement in these patients was not as sudden as that which followed castration, at the end of a few weeks the majority seemed as well in all respects as those patients who had benefited most by castration. In this group we were able to observe a greater degree of regression in the size of the primary prostatic tumor with a corresponding reduction of the amount of residual urine. These beneficial changes appeared to be correlated with and generally in proportion to the amount of feminization brought about. Breasts enlarged and they sometimes became tense and painful. The nipples and areolae turned dark brown. Later there was likely to be an accumulation of weight about the hips. After an average period of seven months, patients treated with stilbestrol relapsed. However, up to the present time, a much smaller proportion of patients have relapsed under stilbestrol therapy than after castration, and those patients who did not relapse after stilbestrol therapy enjoyed excellent health on an average of two years after treatment was begun.

After the castrated patients relapsed, we treated them with stilbestrol, and after the patients treated with stilbestrol relapsed, we castrated them. Although these groups are too small at present for close analysis, neither type of secondary treatment proved successful.

It is of interest to attempt to correlate the chemical and endocrinologic changes with the clinical courses of these patients. Fig. 1 shows the changes which took place in the acid and alkaline phos-

phatases, in the chlorides and calcium of the serum, and in the excretion of the estrogens and androgens of a representative patient following orchiectomy. This man had unusually extensive bone metastases. He did well for eight months and then underwent a clinical relapse with coincident rise in both acid and alkaline phosphatase to pretreatment levels.

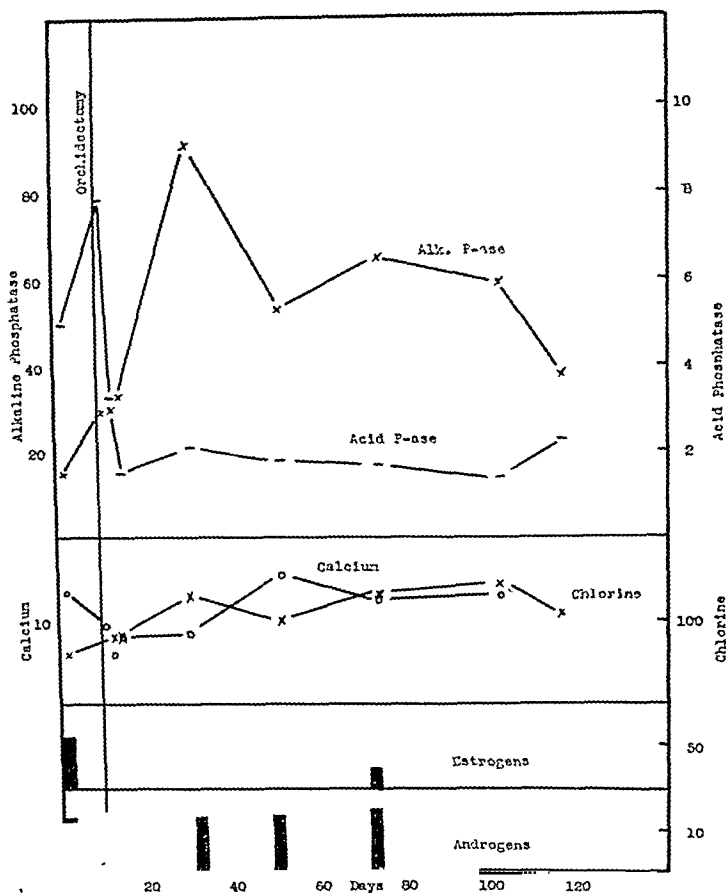


Fig. 1.—Acid and alkaline phosphatase in units per 100 c.c.; calcium in milligrams per 100 c.c., chlorine in milliequivalent per liter; estrogens in mouse units excreted per seventy-two hours; androgens in milligrams excreted per seventy-two hours.

The acid serum phosphatase rose above the initial level on the first postoperative day and then dropped abruptly, but remained above normal throughout the period of observation.

The alkaline serum phosphatase rose rapidly, reaching five times the initial value three weeks after castration, and then exhibited a slow downward trend. During this time the metastatic areas in the bones increased in size, number, and degree of osteoplasia.

The serum protein and inorganic phosphate showed only minor changes and are not shown in the illustration.

The serum calcium dropped to abnormally low values immediately after castration and later returned to normal. This is a frequent finding, the significance of which is not yet apparent.

The serum chlorine paralleled the alkaline phosphatase throughout. This parallelism has been observed in several patients, and may indicate a relation between the adrenals and alkaline phosphatase.

Estrogen assay was unsatisfactory owing to the toxic effect of the urine of this patient on mice, but there is evidence that estrogen excretion fell after castration.

Androgen excretion showed a transitory fall after castration, and then rose to the initial values.

The acid and alkaline phosphatases in the serum of our patients were determined by a modification of the Bodansky method which is described elsewhere. Sodium- $\beta$ -glycerophosphate was used as substrate throughout. Normal values for acid phosphatase were from 0 to 0.7 units per 100 c.c. of serum when the alkaline phosphatase was normal or as high as 0.9 units per 100 c.c. when the alkaline phosphatase was high. Values above 1.0 unit per 100 c.c. were considered pathognomonic of metastasizing prostatic cancer. Normal values for alkaline phosphatase were from 1.5 to 5.0 units per 100 c.c. While increased acid serum phosphatase indicates an extension of a prostatic cancer, a normal quantity of acid serum phosphatase occasionally is found in the presence of an extensive tumor. However, while false negative tests may occur, increased acid phosphatase has not been found except with this disease.

In describing the results of our phosphatase assays, we have omitted patients on whom we had no adequate readings prior to treatment, those who received radiation at such a time as to influence phosphatase determinations, and those who were lost to observation within a month after treatment was started. With these exceptions we have records of the acid and alkaline phosphatases of the serum before and after surgical castration of 26 patients with prostatic cancers.

In 19 of the 26 patients the acid serum phosphatase was elevated before treatment was given. In 16 of the 19 the quantity diminished during the two months which followed castration. While it seldom reached normal, the decrease in acid phosphatase usually was striking, amounting in one case to a change of from 115.0 to 1.4 units. In 3 patients there was no significant change in acid phosphatase after castration. Two of these men failed to show clinical improvement after operation and soon died. In the third, only a borderline abnormality in acid phosphatase was present. Seven patients had a normal acid phosphatase before treatment and no remarkable changes could be observed after castration.

In a group of 23 patients treated with stilbestrol we found changes in acid serum phosphatase similar to those which followed castration.

Our experiences, therefore, confirm Huggins' findings and offer clear-cut evidence that withdrawal of testicular hormones or administration of estrogens, for a time at least, causes a marked reduction of acid serum phosphatase. Presumably this may be brought about either by diminishing the production of acid serum phosphatase by the prostatic cancer or by lessening the ease with which this enzyme enters the circulation. In patients in whom acid phosphatase does not enter the circulation neither castration nor administering stilbestrol causes it to do so.

Of the 26 patients who were surgically castrated, the preoperative assays of alkaline serum phosphatase were elevated in 17. All but 1 of these men had definite evidence of bone metastases. In 11 of the

17 after castration there was a further rise in alkaline phosphatase at some time during the following two months. In the remaining 6 patients the alkaline phosphatase either did not change or it decreased. Sixteen of 22 patients who were treated with stilbestrol had pretreatment elevations in serum alkaline phosphatase. Of these, only 4 showed a further rise in alkaline phosphatase levels; in the remainder there was no change or a slow decrease.

Nine patients had normal preoperative readings of serum alkaline phosphatase. In 4 of these patients there was definite evidence of bone metastases. In 3 of the 4 there was a significant rise in alkaline phosphatase after castration.

In the patients who have been observed long enough for roentgenographic changes to have become demonstrable there usually has been a marked increase in the degree of osteoplasia whenever there has been a rise in the alkaline phosphatase. In some cases this appeared to indicate healing, while in others pre-existing metastatic areas have grown larger and new metastatic areas have appeared. In at least 4 patients in whom a fall in alkaline phosphatase has occurred after an initial rise, the fall apparently has been associated with extension of the metastases. We have been able to find no correlation between changes in either estrogen or androgen output and alterations in either of the serum phosphatases.

Considerable evidence has been produced by one of us (H. Q. W.) and by others to show that alkaline phosphatase is produced in excess by bone as a defense mechanism. This is a nonspecific response, and may be the result of deficient supplies of calcium and phosphorus, as in rickets; of loss of calcium and phosphorus, as in hyperparathyroidism; or of injury, as in metastatic disease. When prostatic carcinoma has invaded bone, the activity of the injurious agent (prostatic carcinoma) is reflected in the degree of elevation of the acid phosphatase in the blood. The activity of the bone defense is indicated by the amount of alkaline phosphatase in the blood.

After castration the activity of the prostatic cancer in bones probably decreases as is shown by the drop in acid phosphatase. We should expect that the alkaline phosphatase, an index of the attempt at bone repair, would also decrease as the need for repair became less urgent, and would reach normal, several months later, when repair was well advanced. This has occurred in a few of our patients. As previously indicated, however, in the majority of cases the alkaline phosphatase rises rather than falls in the first two months after castration. Three possible explanations of this reaction may be suggested:

1. There may be no increase in the production of alkaline phosphatase, but instead there may be an increased rate of diffusion of this enzyme into the blood. This is unlikely in view of the close relationship between assays of alkaline serum phosphatase and bone activity.

However, certain osteogenic sarcomas contain abundant alkaline phosphatase which does not enter the circulation. Hence, there is the possibility that a shift in hormone balance may cause a change in the diffusibility of phosphatase.

2. The rise in alkaline serum phosphatase may indicate the response to increased injury. This is improbable because of the coincidental reduction of pain and decrease in acid phosphatase. However, in some patients metastases have spread in the absence of symptoms and with normal acid phosphatase. Therefore, the possibility of a temporary acceleration of bone injury cannot be dismissed entirely.

3. The shift in hormone balance following castration may stimulate the regenerative capacity of bone. Many investigators have shown that sex hormones may influence bone development although the mechanism remains obscure. While we have been unable to observe a close relationship between changes in alkaline serum phosphatase and variations of estrogen and androgen excretion, it must be remembered that androgen assays measure a number of different 17-ketosteroids which differ in their biologic activity. It is possible that after castration a shift takes place in the relative amounts of these steroid fractions and this may influence the regenerative capacity of bones. Therefore, a definite answer to this problem must await further work on the fractionation of the ketosteroids. It is significant that the alkaline phosphatase response to castration is usually different from that to stilbestrol therapy.

Huggins felt, as a result of his work with dogs, that the prostatic epithelium, whether normal or cancerous, was dependent for its growth on the relation of estrogenic to androgenic hormones in the blood. Estrogens were shown to decrease prostatic secretion, and androgens to increase it in experimental animals. The reason for castrating the man with prostatic cancer, according to this reasoning, was to remove the source of androgens. It has been known for several years that men excrete estrogenic hormones in their urine and since they have no ovaries, the adrenals have usually been thought of as the source of these substances. Since castration was not thought of as affecting the adrenals, the estrogens should remain constant thus bringing about a shift in estrogen-androgen ratio toward a higher estrogen and lower androgen level. Obviously, the administration of estrogens per se would bring about a similar sort of shift.

We were greatly surprised to find that these theoretical changes were not borne out by experimental observations in our laboratories. Twenty-seven cases of cancer of the prostate treated by castration were studied for their precastration levels of estrogen and androgen excretion. The estrogens averaged 16.6 mouse units per twenty-four hours and the androgens 6.1 mg. of androsterone equivalent as determined colorimetrically by the Callow modification of the Zimmerman meta-dinitrobenzene reaction. This is a low value for 17-ketosteroids, the healthy young male excreting 15 to 25 mg. in a similar period.

After castration, instead of estrogens remaining the same and androgens falling as we had expected, the estrogens dropped in all but one of 16 patients tested to a postoperative average of 8.5 mouse units, about one-half the precastration level, while the androgens determined colorimetrically tended to remain the same or rise slightly. The average change was from 6.1 to 7.1 mg. in the 17 patients tested. All postoperative levels were obtained one month or longer after castration. Gonadotropic hormones from the anterior pituitary were assayed before and after castration in 16 patients. Of these, there was a definite postcastration rise in 11, while 5 showed quantities of this hormone too low to measure either before or after castration. No case showed a fall in gonadotropic hormone in the urine postoperatively.

In contrast to these figures are those obtained by assays on 9 men before and after treatment with 2 to 5 mg. of diethylstilbestrol daily. The estrogenic assays on these men averaged 18.2 mg. per twenty-four hours before treatment. Following treatment this figure rose enormously because a certain amount of the diethylstilbestrol was excreted in the urine. The androgens (17-ketosteroids) before treatment averaged 8.9 mg. of androsterone equivalent per twenty-four hours, but after treatment these hormones fell in every case to an average of 5.4 mg. androsterone equivalent.

Of 6 patients studied for gonadotropic hormone excretion rate before and after stilbestrol, in none was there a post-treatment rise. Three showed no measurable excretion either before or after stilbestrol, while the other 3, showing small quantities of hormone in the urine before the administration of the drug, excreted too little to measure after it was started.

From the point of view of hormones excreted in the urine, therefore, the treatment of prostatic cancer by castration differs completely from treatment with diethylstilbestrol. Castration seems to cut estrogenic excretion in half, tends to raise 17-ketosteroid excretion, and to release the pituitary from testicular inhibition so that it pours out its gonadotropic hormone in excessive quantities. Stilbestrol raises the estrogenic excretion rate and decreases both the 17-ketosteroid excretion rate and the quantity of gonadotropic hormone in the urine. It appears that these two methods of treatment, while causing similar favorable clinical effects and the same changes in serum acid phosphatase, differ markedly in their effects on the hormones. These observations may explain why the patient who is having recurrent symptoms following castration is not improved by stilbestrol or the stilbestrol patient by castration, such treatment merely neutralizing the effect of the primary treatment rather than re-enforcing it.

Clarification of the true mechanism by which prostatic cancer regresses after castration or the administration of stilbestrol must await more detailed analysis of the changes produced. The Callow test, for in-

stance, measures all neutral steroids with a ketonic group in position 17 of which there are many. The apparent rise following castration may be in some inactive substance in this group and therefore the contrasting hormone changes between castration and stilbestrol administration may be more apparent than real. The clinical observation that one treatment does not aid a patient who relapses after having received the other is strong evidence, however, that these are opposite rather than similar forms of therapy.

#### SUMMARY

1. About 100 patients with cancer of the prostate have been treated at the Memorial Hospital either by castration or by the administration of stilbestrol given in doses of 1 to 5 mg. daily by mouth. Both forms of treatment have given striking clinical improvement, at least temporarily. Pain is abolished, appetite is increased, and a gain in weight results. These changes following castration are prompt. They occur more gradually with stilbestrol.

2. After an average of seven to eight months the patients are apt to have a return of pain and obvious progression of disease to death. Institution of other treatment, stilbestrol in the castrated patients or castration in the patients treated originally with stilbestrol, fails to affect the unfavorable course of the disease.

3. Some patients, following treatment, continue to remain clinically free from symptoms of prostatic cancer for long periods of time, two years or longer. The number of such prolonged arrests of cancer seems more frequent in the group treated with stilbestrol than by castration, so that this has become our routine initial form of treatment in the last eighteen months.

4. Stilbestrol seems to cause local regression in the size of the prostate and reduction in the amount of residual urine more frequently than castration.

5. Changes in bony metastases in general are toward an increase in calcification. Whether this represents healing of the lesions, a change in their properties, or a spread of tumor is hard to say. Occasionally an increase in roentgen density may be accompanied by the appearance of new shadows not previously visible.

6. Serum phosphatase determinations have proved useful for diagnosis and as a method of following the course of the disease. Elevation of serum acid phosphatase above 1 Bodansky unit is pathognomonic of prostatic cancer, although a low acid phosphatase does not rule out the presence of this disease. Serum alkaline phosphatase is usually elevated when bone metastases are present.

7. Serum acid phosphatase falls promptly in those patients who respond favorably to castration and rises again with a return of cancerous activity. The same changes occur more slowly in patients treated



with stilbestrol. Serum alkaline phosphatase often rises following castration and then slowly falls. The rise is not so apt to be present in patients treated with stilbestrol. The cause of this rise and subsequent fall is unknown. Reactivation of metastatic disease is usually reflected by a rise in serum alkaline phosphatase.

8. Castration decreases estrogenic excretion in the urine and usually causes a rise in androgens as measured colorimetrically as 17-ketosteroids by the Callow-Zimmerman test. It causes a rise in excretion of pituitary gonadotropic hormones in the urine.

The administration of stilbestrol decreases the output of the 17-ketosteroids and the gonadotropic hormone from the pituitary. After its administration the excretion of stilbestrol in the urine gives a marked rise in the estrogen assays.

Our findings suggest that the mechanism whereby castration and stilbestrol cause regression of prostatic cancers is fundamentally different.

#### REFERENCES

- Gomori, G.: Distribution of Acid Phosphatase in the Tissues Under Normal and Pathological Conditions, *Arch. Path.* 32: 189-199, 1941.
- Gutman, A. B., and Gutman, E. B.: "Acid" Phosphatase and Functional Activity of the Prostate (Man) and Preputial Glands (Rat), *Proc. Soc. Exper. Biol. & Med.* 39: 529-532, 1938.
- Gutman, E. B., Sproul, E. E., and Gutman, A. B.: The Significance of Increased Phosphatase Activity of Bone at the Site of Osteoplastic Metastases Secondary to Carcinoma of the Prostate Gland, *Am. J. Cancer* 28: 485-495, 1936.
- Huggins, C., Masina, M. H., Eichelberger, L., and Wharton, J. D.: Quantitative Studies on the Prostatic Secretion. I. Characteristics of the Normal Secretion; the Influence of Thyroid, Suprarenal, and Testis Extirpation and Androgen Substitution on the Prostatic Output, *J. Exper. Med.* 70: 543-556, 1939.
- Huggins, C., and Clark, P. J.: Quantitative Studies of Prostatic Secretion. II. The Effect of Castration and of Estrogen Injection on the Normal and on the Hyperplastic Glands of Dogs, *J. Exper. Med.* 72: 747-762, 1940.
- Huggins, C., and Hodges, C. V.: Studies on Prostatic Cancer. I. The Effect of Castration, of Estrogen and of Androgen Injection on the Serum Phosphatases in Metastatic Carcinoma of the Prostate, *Cancer Research* 1: 293-297, 1941.
- Kutscher, W., and Wolbergs, H.: Prostataphosphatase, *Ztschr. f. Physiol. Chem.* 236: 237-240, 1935.
- Munger, A. D.: Experiences in Treatment of Carcinoma of Prostate With Irradiation of Testicles, *J. Urol.* 46: 1007-1011, 1941.
- Satterthwait, R. W., Hill, J. H., and Packard, E. F.: Experimental and Clinical Evidence of the Role of 17-Ketosteroids in Prostatic Carcinoma, *J. Urol.* 46: 1149-1153, 1941.
- White, J. W.: Present Position of the Surgery of the Hypertrophied Prostate, *Ann. Surg.* 18: 152, 1893.
- White, J. W.: The Results of Double Castration in Hypertrophy of the Prostate, *Ann. Surg.* 22: 1, 1895.
- Woodard, H. Q.: Acid and Alkaline Glycerophosphatase in Tissue and Serum, *Cancer Research* 2: 497-508, 1942.
- Woodard, H. Q., and Craver, L. F.: Serum Phosphatase in the Lymphomatoid Diseases, *J. Clin. Investigation* 19: 1-7, 1940.
- Woodard, H. Q., and Kenney, J. M.: The Relation of Phosphatase Activity in Bone Tumors to the Deposition of Radioactive Phosphorus, *Am. J. Roentgenol.* 47: 227-242, 1942.

## THE RELATIONSHIP OF HORMONES TO TESTICULAR TUMORS

GRAY H. TWOMBLY, M.D., NEW YORK, N. Y.

*(From the Memorial Hospital for the Treatment of Cancer and Allied Diseases)*

**M**ALIGNANT testicular tumors are of tremendous interest both to the endocrinologist and to the oncologist for several reasons. They are a type of tumor which can be produced experimentally either by estrogenic hormones, as in mice, or by chemical irritants and natural or injected hormonal stimulation, as in fowls. Since the testis is one of the endocrine glands, tumors of this organ would be expected to, and as a matter of fact do, produce hormones. By assay of these substances it is often possible to test for the presence of active testicular cancer, even when it is not clinically obvious, and to venture a fairly shrewd guess as to the radiosensitivity of the tumor and the clinical course of the disease. Finally, the possibility of influencing tumors of one of the endocrine glands by administered hormones or changes in the hormone balance is an almost unexplored but fascinating field for the man interested in clinical research. There are several ways of causing atrophy of the normal testis. Will any of these affect the tumorous one?

### HORMONES AND THE PRODUCTION OF TESTICULAR TUMORS

Teratomas of the testis have been produced successfully in roosters by several workers by the injection into the testis of zinc chloride or zinc sulfate, a procedure first carried out in 1925 by Michalowsky. Falin mentions a total of 23 so produced and in his latest articles adds 5 produced by zinc sulfate, 4 by zinc nitrate, and 1 by copper sulfate.

From the endocrinologic point of view the most interesting feature of these tumors is that all workers are agreed that the tumors occur only in the spring when zinc salts alone are given. Bagg, however, was able to produce 2 of his 6 tumors in the summer, one in July and the other in August, by continuous treatment of the fowls with extract of sheep anterior pituitary gland.

The tumors appear to be quite adult in type and resemble some of the so-called adult cystic teratomas seen in men. They are not transplantable and do not produce quantities of gonadotropic hormone sufficient to appear in assays of the blood. In this respect they are similar to their human counterparts.

The fundamental cause of these tumors seems to be the necrosis produced by the zinc or copper salts, although Falin thinks that zinc uniting with some of the protein material of the necrotic testis may form an

"inductor" or "evocator" similar to the "organizer" of Spemann. Bagg suggests a similar hypothesis. The role of hormones in the formation of these tumors seems to be secondary. No tumors have arisen from hormone stimulation alone, although Bagg treated a group of 22 birds in this way. However, the testis appears to be sensitive to the zinc only when it is actively growing under the influence of the host's own hormones in the spring or when stimulated by injected pituitary hormone.

A more direct relationship between tumor production and endocrine stimulation is seen in the testicular Leydig cell tumors of mice produced by prolonged treatment with estrogenic substances. These were described first by Bonser and Robson and by Hooker, Gardner and Pfeiffer. They have occurred only in the Strong A strain and in two other strains derived from it, but have been produced by three chemically different types of estrogens—estradiol benzoate, stilbestrol, and triphenylethylene. The sequence in their production seems to be an atrophy of the tubules and the formation of three different generations of Leydig cells. Tumors arise from the second or third generation. They are malignant and metastasize widely. Many appear to be functional, stimulating the seminal vesicles, an observation which suggests that they elaborate male hormone.

Leydig cell tumors in man are of great rarity, only 9 authentic cases having been reported. They appear to produce premature puberty when they occur in young boys, but no symptoms of an endocrine nature are described occurring in older men. We have seen 1 case recently occurring in an adult, and he had no gross sexual abnormalities or symptoms. Unfortunately, the nature of the tumor was not recognized until after it had been removed so that no assays for male hormone output could be carried out.

The precocious puberty in boys and the lack of symptoms in men would fit in with an overproduction of male hormone by this type of tumor, as is thought to occur in the mouse, for such an excess would be readily apparent in the undeveloped male but would probably show no effect in the adult male. There is no hint in the literature of a possible excess of estrogenic stimulation as the etiologic agent in the cases of this type of tumor in man.

There is some evidence from clinical observation that the more common teratoma of the testis in man also may have an endocrinologic etiology. For instance, it is a well-known fact that teratoma testis occurs much more frequently in men with undescended testicles than in the general male population. The incidence of cryptorchidism is given as 0.23 per cent in Army records, whereas 11 per cent of 7,000 recorded cases of cancer of the testis occurred in unilateral or bilateral cryptorchids. In a series of 203 cases of teratoma testis studied by us, 27 or 13.3 per cent were in men with cryptorchidism. That this high incidence is not related to trauma to the organ in the inguinal canal is

suggested by the figures of Gilbert and Hamilton who found 345 of 835 reported malignant testes to be intra-abdominal where they could not be readily damaged. Eleven per cent of these 345 occurred in pseudohermaphrodites, a finding that again suggests a hormonal etiology for the tumor.

Not all tumors occurring in patients with cryptorchidism arise in the undescended testicle. In Gilbert and Hamilton's series, 23 of 744 patients with unilateral cryptorchidism had the tumor in the normally descended organ. Six in our own series of 27 occurred in the normal testis. That this may happen more frequently than is shown by Gilbert and Hamilton's figures is suggested when it is considered that their data were taken from cases reported in the literature. It would seem probable that authors would be more apt to mention cryptorchidism when it affected the cancerous testicle than when it was found on the opposite side and appeared to have no direct connection with the tumor.

Another observation which points to a connection between hormones and the formation of teratomas in men is that these tumors, like those in the rooster, arise most frequently during the active sexual life of the patient. Unlike other forms of cancer, in which the peak in incidence is apt to fall after the age of 45, teratoma testis occurs in comparatively young men, the highest percentage lying in those between the ages of 35 and 39. If one compares the percentage of teratoma testis in the various age groups with the percentage of living males in the same age group, one finds more testicular cancers between the ages of 20 and 54 than one would expect were they distributed uniformly according to the number of males in each age group in the general population.

A third point of some interest in this connection lies in the finding of abnormal amounts of pituitary hormone in the urine of about 75 per cent of patients with teratoma, particularly of the unicellular or seminoma type. As has been shown by Hamburger and by our own experience, this hormone may be excreted in the urine in fairly large quantities without any clinical evidence of active testicular tumor being demonstrable. One may try to explain its presence as due to liberation of the pituitary from testicular control either because of destruction of one testis by tumor, roentgen therapy, or operative removal, but such an explanation does not account for the failure of the remaining testicle to suppress pituitary overactivity. Certainly the removal of one ovary in the female is not followed by the menopause. Why should the removal of one testicle have a different effect in the male?

Hamburger has shown this increased output of follicle-stimulating hormone from the pituitary to be accompanied by a decreased output of male hormone as tested on the comb of the capon. Is it possible that this shift in hormone balance with decrease in androgens and increase in pituitary gonadotropin is a primary condition which leads later to the formation of a malignant testicular tumor? It is obviously not possible

to answer such a question at present for no opportunity has arisen to observe a patient with such a hormonal change and to determine whether he later developed teratoma.

#### EXCRETION OF HORMONES BY MEN WITH TESTICULAR TUMORS

*Gonadotropic Hormones.*—That men suffering from testicular tumors may excrete large quantities of gonadotropic hormone was demonstrated by Zondek in 1929 and 1930, in 2 cases reported by him. It was confirmed the same year by Heidrich, Fels, and Mathias and later by Ferguson, Downes, Ellis, and Nicholson. Because the nature of the gonadotropic hormones was not well understood at first, certain errors have crept into the literature on the subject and have caused great confusion. Ferguson thought that there was only one hormone in urine from men with testicular tumors. This substance, in small quantities, caused the ripening of the Graafian follicles of the ovaries of infantile female rats or mice. When it was injected in five times the amount which gave follicle ripening, corpora lutea atretica were formed. Engle, and Evans and Simpson, among others, pointed out early that the gonadotropic hormone of pregnancy urine did not give the same reaction as extracts or implants of the anterior pituitary. However, Hamburger was probably the first to demonstrate clearly the differences in the reactions produced by pregnancy urine and urine from castrates or women past the menopause. Evans and his co-workers studied the type of hormone excreted by a patient with teratoma testis and came to the conclusion that it resembled that found in pregnancy urine in some respects and anterior pituitary extract in others. Fevold, Fiske, and Nathanson examined urine from another patient with chorioepithelioma testis and found it to give identical reactions in male and female rats, hypophysectomized rats, and male and female pigeons with pregnancy urine. Several other workers carried out similar tests (Fluhmann, Freed, and Main), but it remained for Hamburger to study a number of such patients and find that the type of hormone present was not constant. Some patients excreted chorionic gonadotropin as these investigators had said. Some, on the other hand, excreted the castrate type of gonadotropin, follicle-stimulating hormone, and some excreted a combination of the two.

As long as one thought of the hormone as of one type and produced by the tumor, it seemed logical to suppose that destruction of the tumor would result in disappearance of the hormone. Ferguson thought his material warranted such a conclusion, but later workers have found this hypothesis to be unreliable (Twombly, Temple, and Dean). Many tumors occur, metastasize, and kill the patient without showing any gonadotropic hormone at all in the urine.

It was noted by Ferguson that untreated tumors of approximately the same extent or with the same amount of metastases excreted varying

quantities of hormone. He explained this by saying that the amount of hormone excreted depended upon the type of tumor present and described very definite levels as characteristic of various histologic varieties. This also has proved only partially true. More extended study has shown a tendency for the more malignant embryonal adenocarcinomas and chorioepitheliomas to excrete large quantities of the chorionic type of gonadotropin; but many exceptions are found, widespread adenocarcinoma showing very little or no hormone, while some embryonal carcinomas (seminomas) show large amounts.

Hamburger, Bang, and Nielson also made an attempt to correlate gonadotropic hormone excretion with the histologic appearance of the tumor but laid the emphasis on the type of the hormone rather than the amount. They divided their cases into mixed epithelioma, seminoma, and polycystic teratoid mixed tumors, and maintained that the first was radioresistant and excreted the chorionic type of gonadotropin while the second and third excreted the castrate type, follicle-stimulating hormone. Seminomas excreting follicle-stimulating hormones were radiosensitive.

Hamburger admits that in 75 cases of testis tumor, he found 2 classified histologically as seminomas which nevertheless excreted large amounts, 1,000 and 50,000 M.U. per liter, of chorionic gonadotropin. These he labels pseudoseminoma; that is, they were tumors histologically of the unicellular type which behaved clinically and hormonologically like the mixed epithelioma type. He also lists 4 out of 21 mixed epitheliomas which excreted no hormone or only traces.

Recently Furuhjelm, studying the type of hormone excreted in 65 cases, has found this discrepancy also. Of 29 seminomas, 7 excreted no measurable hormone, 12 follicle-stimulating hormone, 5 chorionic gonadotropin, and 4 both types of gonadotropin. Of 7 malignant mixed epitheliomas, 6 excreted chorionic gonadotropin and one the castrate type of gonadotropin, follicle-stimulating hormone.

In our own laboratory, since 1936, we have attempted to distinguish the two types of hormone in all cases assayed. In these five and one-half years there have been 135 patients on whom complete clinical records are available. Of these, 65 are known to have had active tumor at the time at least one of the tests was run. Thirty-eight cases showed chorionic gonadotropin. Of these, 10 were reported by the pathologist as embryonal adenocarcinoma, and 7 as chorioepithelioma, tumors included under the name mixed epithelioma by Hamburger. Nine cases were embryonal carcinoma or embryonal carcinoma with lymphoid stroma (seminoma). In 7 there was no pathologic report. Two showed complete destruction of the tumor by x-ray before it was removed for pathologic study. Three cases showed mixtures of seminoma and embryonal adenocarcinoma.

Eighteen cases showed follicle-stimulating hormone only. Two of these were chorioepitheliomas, 7 were seminomas, 2 had no pathologic report, 3 were completely destroyed by x-ray before removal, 3 were adult cystic teratomas, and 1 was a mixture of seminoma and embryonal adenocarcinoma. No case of pure embryonal adenocarcinoma was found excreting the castrate type of gonadotropin only.

Finally, there were 7 cases in which no demonstrable gonadotropic hormone was excreted (below 50 to 100 M.U. per day). These included 1 case of embryonal adenocarcinoma, 2 seminomas, 1 with no pathologic report, and 3 showing complete x-ray destruction.

Our experience, then, confirms that of Furuhjelm—that one cannot tell surely the histologic type of the tumor by the type of gonadotropic hormone found in the urine. In this respect we disagree with Hamburger. However, in general all agree that the chorionic type of hormone is more typical of embryonal adenocarcinoma or chorioepithelioma (mixed epithelioma of Hamburger), while the castrate type of hormone is apt to be associated with seminoma (with frequent exceptions).

One point is worth noting in our material. That is that many of the 135 patients not included among the 65 known to have tumors when urinary tests were done were patients treated by orchiectomy elsewhere and sent to us for prophylactic irradiation of the lymph node drainage areas. Many of these showed the castrate type of hormone. Undoubtedly a number had active metastases from a seminoma which never appeared clinically because of the radiosensitivity of this tumor and its consequent destruction. In all probability the number of seminomas associated with the castrate type of hormone should be higher than our figures indicate.

When one examines the histologic preparations of these tumors, the types of tissue that one sees are so different that it is hard to free oneself of the idea that the chorionic type of hormone must be elaborated by one special type of tissue. The frequent association of high titers of this hormone noted by Hamburger, Furuhjelm, and us with embryonal adenocarcinoma suggests more than a chance occurrence. It is my own theory that the explanation for the discrepancies in which seminomas are associated with the pregnancy type of hormone is to be found in the fundamentally teratoid nature of all these tumors emphasized by Ewing. Four cases mentioned previously are of especial importance in this regard. These are the ones in which both types of tumor were found in the same testis. Often, the two types of tissue lay side by side in the same section, separated by only a thin fibrous septum. Testicular tumors are often large, and it is the accepted pathologic custom to take a few small representative sections from such a tumor in routine work. If the whole tumor were fixed and studied by large serial sections or many small sections, it is our belief that the correlation be-

tween the presence of chorionic gonadotropin in the urine and embryonal adenocarcinomatous tissue in the tumor would be much closer.

*Prognostic Significance of Gonadotropic Hormones:* Zondek pointed out in 1935 that any marked increase in excretion rate of prolan particularly of prolan B is an unfavorable sign and usually indicates metastases. The urine in 12 cases he studied showed corpus luteum formation in the test mice in 5, either with fresh urine or when concentrated. Three of these were dead when he wrote and the other 2 were not followed.

Hinman, who still fails to differentiate different types of gonadotropic hormones in teratoma urines, almost echoes Zondek in his latest article in which he says, "It is our experience that all of these patients with abnormal amounts of hormone in the urine have a poor prognosis and that most of them die of cancer within a year regardless of roentgenotherapy."

Hamburger makes a very clear distinction between the two types of hormone from the point of view of prognosis. He believes that the chorionic type is made by the tumor because this material has the same biologic properties as the hormone found in pregnancy urine which is thought to come from the placenta. A second argument for the origin of the hormone in the tumor is that there is a large amount of hormone in the tumor tissue and little or none in the pituitary gland. Finally, there seems to be a close relationship between the amount of hormone in the urine and the amount of active tumor tissue present in the patient's body. To this we might add a fourth observation: that we have never observed this type of hormone in male urine except when tumor tissue was known to be present or later proved to be so. Hamburger points out that the presence of this type of hormone is associated with a radioresistant type of tumor. "In all cases which have been under observation for a sufficiently long time, there have developed metastases, resistant to x-ray treatment, and all the patients died in a comparatively short time."

Furuhjelm agrees with this statement. In his own cases, 14 showed chorionic gonadotropin in the urine, of whom 6 were already dead at the time of his report, 4 living with metastases, and on 4 there was no note of their clinical condition.

We have found Hamburger's contention most correct in our own series of 135 cases. First, in no case was chorionic hormone present without active tumor. We believe with Hamburger that this hormone is a product of the tumor tissue itself and this is further evidenced by one patient who showed large amounts of hormone on his first test, which disappeared at once after orchiectomy. There have been 38 patients who showed this hormone and of these, 32 are dead. Four are still alive with active disease. The 2 remaining are alive and apparently free of disease. One is the patient mentioned previously, cured by simple orchiectomy;



the other has received a great deal of x-ray therapy and has stayed well for the three years preceding this report. The hormone in his urine has changed from small amounts of chorionic gonadotropin to moderate amounts of follicle-stimulating hormone.

Hamburger points out that the castrate type of hormone may be present with no evidence of active tumor and that it does not vary in amount with treatment of the tumor or extension of the cancer.

Again our experience is in complete agreement with this finding. In fact, it was the clinical observation of several patients who were excreting 1,000 M.U. of hormone per day, although they had been clinically free of cancer and without treatment for several years, which first drew our attention to the value of differentiating the types of gonadotropin.

*Methods of Differentiating Gonadotropic Hormones of the Castrate From the Chorionic Type:* Many different methods have been used to differentiate the different types of gonadotropin. The more practical ones are open to the objection that they use intact animals in which the action of the animal's own anterior pituitary may play a part. It has been pointed out by Hinman that only in hypophysectomized animals is this objection ruled out. If one gives castrate urine extract to a young hypophysectomized female rat, marked follicle ripening in the ovaries is brought about. Chorionic gonadotropin, on the other hand, causes merely a luteinization of the theca cells and, at least in small doses, no follicle formation. Such animals have been used in testing a few individual urines from patients with testicular tumors (Fluhmann, Fevold, and others). These have been patients excreting chorionic gonadotropin in large quantities. No investigator has used hypophysectomized animals routinely because of the difficulty in obtaining such test animals in any quantity.

Various types of birds may offer means of differentiating gonadotropic hormones. For instance, the common English sparrow in the eclipse plumage of the fall and winter responds by blackening of the bill to pituitary hormones but shows no such reaction to pregnancy urine. Male African weaver birds show blackening of the white breast feathers on injection with luteinizing hormone from the pituitary but not from follicle-stimulating hormone. Hamburger has used infantile cocks very successfully in differentiating hypophyseal from chorionic hormone. Again Lahr, Riddle, and Bates have shown increase in the weight of the testis in doves or the ovaries of pigeons from pregnant mare serum or anterior pituitary extract, an effect not produced by pregnancy urine.

Fevold has reported quantitative extraction of chorionic gonadotropin by trieresol, and destruction of the follicle-stimulating hormone of castrate urine by the same process.

The most practical method of differentiating the hormones is by the use of infantile female rats and mice. In these animals there are a number of differences which allow one to tell which hormone has been

injected. The most obvious and easiest is the difference in the morphology of the ovary itself and for this purpose mice are superior to rats since little spontaneous ripening occurs in animals under 9 Gm. in weight. Pregnancy urine given in dilutions just strong enough to give a positive reaction will cause the maturation of one or two large Graafian follicles. Along with this one sees a ballooning of the uterus with watery fluid. Larger doses result in the formation of one or many corpora lutea atretica. Sometimes this reaction is accompanied by Zondek's reaction II, the formation of corpora hemorrhagica.

Castrate urine, on the other hand, causes the ripening of many or all the follicles present. Either no corpora lutea are formed or only with very high dosage. While in borderline cases it may be hard to distinguish the two types of reactions, when one has looked at a few examples of each, it is surprisingly easy to distinguish them in most instances. This is particularly true if sets of ovaries from animals injected at different levels are available for histologic study. The uteri of animals injected with castrate or menopausal urine are hypertrophied but not dilated.

A few cases have been described in which the urinary gonadotropin resembled that found in pregnant mare serum. The presence of this type of hormone is characterized by the typical picture in the ovary produced by castrate urine when a small dose is given. However, when slightly larger doses are given, multiple corpora lutea appear. That this gonadotropin is a mixture of the chorionic with the castrate type, and not identical with pregnant mare serum hormone, has been demonstrated by injecting it into rabbits. Mare serum hormone so treated is either destroyed or excreted in very small amounts. The substance produced by these rare cases of testicular tumor was excreted in amounts of 20 per cent of the injected total.

Chorionic gonadotropin may be distinguished from follicle-stimulating hormone in another way. If increasing doses of pregnancy urine are given to infantile female rats 26 to 28 days old and the ovaries weighed after 100 hours, the ovarian weights will be found to increase very slowly until doses in the neighborhood of 10,000 times the minimal effective dose are reached, when there will be a sharp rise. Castrate or menopausal urine gives a sharp, prompt rise to maximal weights with doses of only two to four times the minimal effective dose. Many urines from teratoma of the testis have been studied in this way by constructing dose response curves with infantile female rats. In all cases those showing the chorionic type of follicle ripening and corpus luteum formation have given curves identical with pregnancy urine gonadotropin, while those showing follicle-stimulating hormone by mouse ovarian morphology have given the menopausal type of rat ovarian dose response curve.

There is another differentiating reaction between the two types of hormones in human urine, and that is the relative sensitivity of the rat

and the mouse to each. When chorionic gonadotropin is present in the urine, the infantile female rat is about five times more sensitive than the infantile mouse, whereas the production of estrus with follicle-stimulating hormone from castrate or menopausal urine requires two to three times more hormone in the case of the rat than in the mouse. This last reaction has been used very little to distinguish these substances from one another.

In our own laboratory we have confined our efforts in distinguishing the hormones to the morphologic differences they produce in the ovaries of infantile female mice, 21 days old, weighing 7.5 to 9 Gm. These animals are injected in lots of 6, each animal receiving a different quantity of fresh urine or alcohol concentrate as follows: Three are injected with 0.1, 0.2, or 0.4 c.c. of fresh urine on each of five occasions within forty-eight hours. The other 3 receive similar amounts of a  $\times 5$  alcoholic concentrate. This is made by precipitating 40 c.c. of urine with 200 c.c. of 95 per cent ethyl alcohol, collecting the precipitate, washing twice with ether, drying, and redissolving in 8 c.c. of water. The animals are killed at 96 to 100 hours and the ovaries examined grossly for follicles and corpora lutea. If either are found in any animal, groups of 5 mice are injected with the lowest quantity producing the original reaction, one-half this amount, and double the amount. That is, the reaction is checked on groups of 5 animals at, above, and below the original test dose. The ovaries of this set of animals are fixed, sectioned, stained, and studied under the microscope. We have noticed that the formation of corpora hemorrhagica occurs only in the ovaries of animals injected with urine containing the chorionic type of gonadotropin, at least in our experience.

#### EXCRETION OF ESTROGENS BY MEN WITH TESTICULAR TUMORS

Hamburger investigated the estrogenic excretion rate of 23 men with testicular tumors. Of these, 10 had seminoma, of whom 9 showed normal rates and 1 a slightly increased amount. One pseudoseminoma showed increased amounts of chorionic gonadotropin and slightly elevated estrogenic excretion. Of 8 mixed epitheliomas, 1 showed no estrogens, 2 were normal, 3 moderately elevated, and 2 markedly elevated. There was a direct correlation between the amount of chorionic gonadotropin and the increase in total urinary estrogen excretion. The 3 highest estrogenic values were in urines containing more than 100,000 M.U. of chorionic hormone per day.

In our own laboratory only one patient has been studied for his estrogenic excretion rate. This man had a widespread chorioepithelioma, arising in the testis, with well-marked gynecomastia. He showed very marked elevation of urinary estrogens over normal men.

The suggestion immediately presents itself that the tumor itself is responsible for the production of estrogens as well as gonadotropin and that the increased estrogen titers are directly related to the gynecomastia

seen in cases with widespread active disease. However, there seems to be another type of gynecomastia which occurs in patients with no evidence of humor, possibly as a hemicastration effect. Gynecomastia has often been thought a bad prognostic sign, and this is undoubtedly true when it is associated with high chorionic gonadotropin, but in 6 of the 12 cases observed by us, there was no such correlation and the patients did well.

In contrast to our own findings and those of Hamburger are those of Smith and Smith, who found low urinary estrin levels in 4 cases of chorioepithelioma, 3 in men and 1 in a woman.

#### EXCRETION OF PROGESTERONE BY MEN WITH TESTICULAR TUMORS

As far as we are aware, the only patient studied for this possible excretion of progesterone or its metabolic product, pregnandiol, is one seen in our own laboratory. This man, with a chorioepithelioma of the testis, was found to excrete from 10.5 to 16.5 mg. per forty-eight hours of a substance identified by its melting point and mixed melting points as probably free pregnandiol.

#### EXCRETION OF ANDROGENS BY MEN WITH TESTICULAR TUMORS

Because he found no evidence of a decreased estrogenic excretion rate which might account for the increased output of the castrate type of gonadotropin in 75 per cent of the patients with seminoma, Hamburger sought for a decreased testicular function as determined by a decreased male hormone excretion in the urine. In this he was successful. Of 19 cases of seminoma in which urine was assayed by direct application of a urinary extract to the combs of white Leghorn capons, 15 showed a moderate to marked decrease in total biologically active androgens. The average excretion rate for all 19 was 10 I.U. per day as compared with 50 I.U. for normal young and middle-aged men without tumors. Twelve other men with tumors causing the excretion of chorionic gonadotropin were tested, of whom one-half had normal androgenic values. The other 6 were below normal. He suggests that the formation of a large quantity of chorionic gonadotropin may stimulate the other testis or the adrenals to the production of male hormones and so explain the difference in output between the two types of tumors. Hamburger thinks the low output of male hormone is due to damage or removal of the affected testis, and that this in turn releases the pituitary which puts out the increased amounts of follicle-stimulating hormone found in the urine. As pointed out in the early part of this article, one may consider these changes as the cause rather than the result of the tumor.

In the case previously referred to and assayed for male hormone by the colorimetric method of Callow, a high normal (24 mg. androsterone equivalent per 24 hours) was found while the biologic activity of this material tested on the chick comb was low (3.1 mg. androsterone equivalent per 24 hours, 31 I.U.—normal = 20 to 100, average 50 I.U.).

## THE TREATMENT OF TESTICULAR TUMORS WITH HORMONES

As far as we are aware, our own have been the only efforts along this line of therapeutic endeavor. The first possibility that presented itself was the administration of an antigonadotropic hormone. We were supplied\* with some highly potent antigonadotropic goat sera. These were administered to 2 patients with high titers of chorionic gonadotropin in the urine, in the expectation that the amount of hormone would fall. Instead, it rose.

Similar attempts were made with pregnancy and placental blood sera in another case, since several authors believed this fluid to contain substances antagonistic to the growth of chorionic tissue. Again there was a rise in hormone titer, and it was possible to show that this rise and that observed with goat serum were both probably nonspecific serum reactions.

Lately, Huggins' work on cancer of the prostate has awakened the hope that changes in hormone balance may give regressions in cancers of endocrine-controlled organs. Large doses of estrogens in animals produce testicular atrophy. Will they do anything to testicular tumors? So far we have tried it on 2 patients without any clear-cut success, but in neither case was the administration continued long enough. The possibility still remains that this or some similar form of therapy may be effective.

## SUMMARY

1. Teratoma testis has been produced in the fowl by the injection of zinc or copper salts when the testis was simultaneously stimulated by the animal's own or injected hormones.

2. Leydig cell tumors have been produced in mice with estrogens.

3. Certain facts about teratoma testis cases in man suggest an endocrine etiology. These are the frequent occurrence of teratoma in patients suffering from cryptorchidism or pseudohermaphroditism, occasionally in the descended testicle, the high incidence of this type of tumor during the period of greatest sexual activity, and the finding of high levels of the castrate type of gonadotropin, follicle-stimulating hormone, and low levels of androgenic hormones in the urine of patients with testicular cancer, particularly seminoma. These last-mentioned changes do not appear to be dependent upon the presence or absence of active tumor.

4. The gonadotropic hormone found in the urine of men with testicular tumors appears to be of two kinds, chorionic gonadotropin identical with the gonadotropin of pregnancy urine, and follicle-stimulating hormone similar to that found in castrate or menopausal urine.

5. Chorionic gonadotropic hormone is found in the urine only when active tumor tissue is present. It is associated with all varieties of

\*Through the kindness of Dr. A. S. Parkes.

teratoma, but certain observations suggest that it may be produced by the tissue spoken of as embryonal adenocarcinoma and that when it appears in cases of seminoma, this is a further proof of the essential teratoid nature of all such tumors. It is likely that the other type of tissue would be found to be present were a thorough search of all cancerous tissue present in the body to be made.

6. The presence of chorionic gonadotropin in the urine usually means that the tumor will be radioresistant and the patient will die in a short time. Thirty-two of 38 such patients in our own series are dead. Four are living with metastases. Only 2 are apparently cured.

7. Chorionic gonadotropin can be distinguished from follicle-stimulating hormone by its action on the ovaries of hypophysectomized female rats, by its failure to act in certain birds, by its different properties when mixed with trieresol, and by the difference in histologic picture and in ovarian weight when it is injected into infantile female rats or mice. From a practical laboratory point of view, the two hormones are most easily distinguished by the differences in the histologic appearances of infantile mouse ovaries when the animals have been injected with fresh or concentrated urine.

8. Those teratomas which produce large quantities of chorionic gonadotropin also seem to excrete abnormally high levels of estrogens. They may excrete pregnandiol.

9. Teratomas of the testis, especially those classified as seminomas, are apt to show very low levels of biologically active androgenic hormones in the urine.

10. The testicular tumors would seem to offer a tempting field for possible therapy by hormone administration.

## ADRENAL CORTICAL TUMORS—PHYSIOLOGIC CONSIDERATIONS

ALLAN T. KENYON, M.D., CHICAGO, ILL.

(*From the Department of Medicine, University of Chicago*)

### INTRODUCTION

THE student attempting a systematic exposition of the means by which adrenal cortical tumors disorganize the physiologic economy of their hosts is thinking and often guessing well before his proper time. The data he must deal with are still fragmentary and often incongruous. His dubious recompense lies in the circumstance that he may cherish his favorite speculation for a long while before yielding to the hard, new, incontrovertible fact.

For a generation or more the arresting transformations of the human body induced by the secretions of these tumors have been known in some detail and have transcended experimental experience. It had never been possible until recently to secure an adrenal agent of such purity and potency that its effects in heavy, protracted dosage in animal and man could be compared with the phenomena seen in patients. Indeed large amounts of life-sustaining adrenal extracts were so well borne by animals that little support accrued to any notion that excessive amounts of normal adrenal "hormone" would prove disadvantageous. Furthermore, it was never possible to contrast suprarenal failure as seen in Addison's disease with presumed hyperadrenal states in a sufficiently clear and uncomplicated fashion. The diversity and the bizarre character of the defects in the victims of adrenal tumors were far too great. Accordingly, no theory conceiving of one as due to the deficiency of a single hormone and the others as due solely to the excess of that same hormone has been seriously entertained. The clinical expressions of adrenal hyperfunction remained mysterious phenomena beyond experimental realization and at the limits of speculative grasp.

During recent years, however, progress in steroid chemistry has permitted the isolation of a multitude of compounds from the adrenal cortex, the chemical characterization of many, and the partial synthesis of a few. The physiologic properties of these substances are often so different that it has seemed hardly likely that any one of them can represent *the* adrenal hormone.<sup>1, 2</sup> In any event, the mere presence of numerous compounds with various propensities introduces the possibility that each may contribute in its own special manner if discharged to the

organism by a tumor. Familial relationships between adrenal cortical steroids and those from the gonads, indeed the presence of several sex hormones in the adrenal cortex, have served to make the intermixture of sexual and nonsexual symptoms in adrenal disorders more comprehensible. The way is now open for the systematic study of the effects of excessive amounts of adrenal derivatives with the expectation that many of the manifestations of adrenal tumors can be reproduced with acceptable verisimilitude and with justice to the variety of disease.

I intend to outline this pattern of contemporary research bearing upon adrenal hyperfunction, and to interpret the signs and symptoms of the victims of adrenal cortical neoplasia in terms of the properties of adrenal steroids and their chemical relatives in so far as I can. Such interpretations will inevitably be tentative, clumsy, and often erroneous, as much decisive work lies in the future.

#### THE NATURE OF THE COMPOUNDS ISOLATED FROM THE ADRENAL CORTEX

The greater part of our knowledge of the chemical nature of the steroids obtained from the adrenal gland is due to the work of Reichstein and his associates in Switzerland; Kendall, Mason, Wintersteiner, Pfiffner and their associates in this country and Beall in England. These developments have been fully treated in the reviews of Reichstein and Shoppee<sup>2</sup> and Pfiffner.<sup>3</sup> These and several accounts by Kendall<sup>1, 4-6</sup> give much detail concerning the relationships between chemical structure and biologic response. Long's review<sup>7</sup> is especially valuable for its analysis of the effects of cortical compounds on carbohydrate and protein metabolism, and his article with Katzin and Fry<sup>8</sup> for an analysis of the comparative roles of the adrenal cortex and the hypophysis in carbohydrate metabolism. Ingle's review,<sup>9</sup> chiefly of biologic response in general, is well designed to stress many of the infinite number of incompletely answered questions in adrenal physiology. These accounts will be drawn on heavily in the following.

Twenty-eight steroids have now been isolated from the adrenal gland and the structure of all but one determined with considerable certainty.<sup>2</sup> The majority of these, including all possessing properties in any way distinctive of adrenal cortical function, share the 21-carbon skeleton typified by allo-pregnane (I) or  $\delta$ -4 pregnene (II). Biologic activity of adrenal character has been most clearly ascribed to those members of the latter series bearing a ketonic group at carbon 3. By virtue of the side chain attached to carbon 17 the compounds with properties distinctive of the adrenal cortex are closely related to progesterone (III), and differ thereby from the typical androgens and estrogens, as illustrated by testosterone (IV) and estrone (V). Indeed, progesterone itself has been found in the adrenal and bears an intimate functional relationship to the more characteristic adrenal steroids in that it will, unlike either androgens or estrogens, protect both rat and ferret against death after



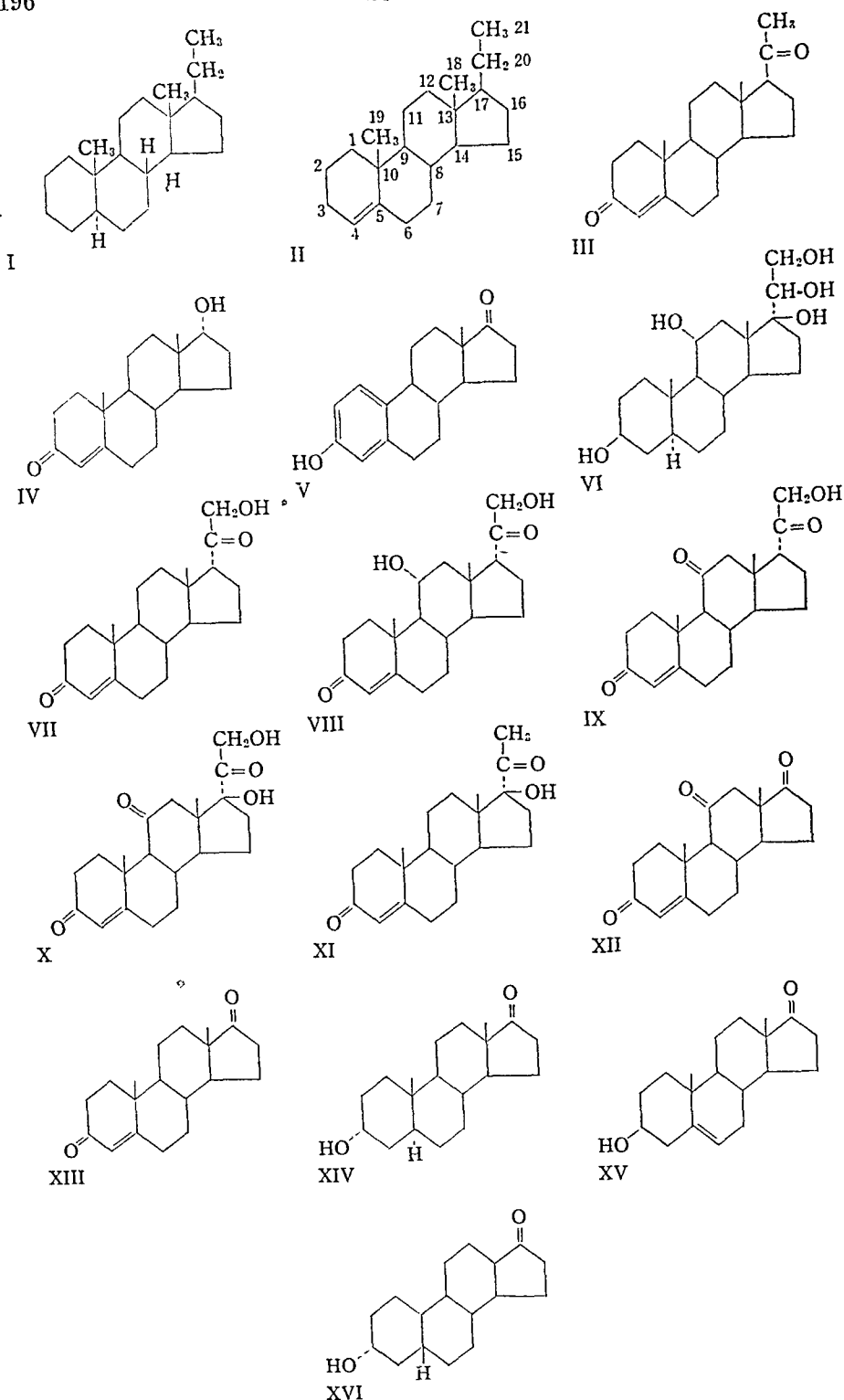


Fig. 1.—(For legend see opposite page.)

adrenalectomy when given in sufficient dosage. No place for progesterone as an adrenal secretion, however, has as yet been found. The remainder of the adrenal steroids capable of repairing suprarenal insufficiency in the ordinary sense seem devoid of progestational, androgenic, or estrogenic properties to a material, functionally significant degree as far as is now known. Instances exist, as in the progestational effects of large amounts of desoxycorticosterone, in which a typical gonadal influence may be simulated. Such reactions may require consideration in some future interpretation of the response to large amounts of secretion delivered by neoplasms. For the time being they have not entered into physiologic calculations. Certain other influences of the steroid hormones, notably the induction of sodium, chloride and water retention, and the depression of thymic growth, are shared, at least to some extent, by gonadal and typical adrenal steroids and do require detailed assessment in the interpretation of normal processes. They represent physiologic reflections of the chemical consanguinity between adrenal and gonadal hormones.

Most of the compounds isolated from the adrenal cortex have been assayed by some test indicative of adrenal insufficiency. By such tests, several of the pure steroids, as for example, allo-pregnane  $3\beta$   $11\beta$   $17\beta$   $20$  (?)  $21$  pentol (VI), have been inactive. The review of Reichstein and Shoppee describes these compounds in detail. For the present, one is disposed to regard them as progenitors or derivatives of the true adrenal secretions, seeking roles for them somewhere in the intrinsic metabolism of the gland itself. As will appear subsequently, however, many phenomena appear in the victims of adrenal tumors which are not as yet fully accounted for by properties of the adrenal steroids now deemed biologically active. Further examination of the supposedly inert compounds in the light of such phenomena must be undertaken.

Desoxycorticosterone (VII) which differs from progesterone (III) only in the presence of an alcohol group at carbon 21, has been isolated from the adrenal itself,<sup>2</sup> but appears to be present in such small amounts as to be often undetectable.<sup>4</sup> This fact while creating a presumption against its being a hormone is not conclusive. The partial synthesis of this compound by Steiger and Reichstein has made it available for physiologic and clinical study in adequate amounts. It is used, thus,

Fig. 1.—Adrenal steroids and related compounds. Enumeration of the carbon atoms given for II,  $\delta$ -4 pregnene. Stereoisomerism indicated by dotted or straight lines according to the conventions discussed by Reichstein and Shoppee. The attached methyl groups are given only for I and II. Otherwise, point of attachment is indicated by straight lines at the junction of two rings.

I	Allo-pregnane	IX	Dehydrocorticosterone
II	$\delta$ -4 pregnene	X	17-hydroxy-11-dehydrocorticosterone
III	Progesterone	XI	$17\beta$ hydroxyprogesterone
IV	Testosterone	XII	Adrenosterone
V	Estrone	XIII	Androstenedione
VI	Allo-pregnane $3\beta$ $11\beta$ $17\beta$ $20$ (?) $21$ pentol	XIV	Androsterone
VII	Desoxycorticosterone	XV	Dehydroisoandrosterone
VIII	Corticosterone	XVI	Etiocolan $3\alpha$ ol $17$ one

largely as the acetate. Its most dramatic effects are upon electrolyte and water metabolism. It corrects the urinary loss of sodium, chloride, and water and the retention of potassium, characteristic of suprarenal insufficiency in several species.<sup>10, 11</sup> While such renal influences are readily measured and are of great importance to the organism, less well-defined modifications of the internal distribution of these electrolytes and water are not to be ignored. Since perversions of electrolyte and water metabolism are fatal to most animals whose salt intake is limited and who are not otherwise subjected to special stress, desoxycorticosterone or its acetate is most effective in maintaining the lives and apparent health of such animals. Indeed, Kendall estimates that as little as 15 micrograms per kilogram per day will suffice for the adrenalectomized dog. Thorn and his co-workers<sup>12</sup> find that patients with Addison's disease may need from 1 to more than 10 mg. of the acetate per day when injected intramuscularly in sesame oil, the vast majority requiring from 1 to 5 mg. per day. Only 60 per cent of this amount is necessary when the steroid is absorbed more slowly from subcutaneous crystalline implants. In contrast to this, corticosterone (VIII) is required by the dog in amounts of approximately 100 micrograms per kilogram per day and is distinctly less effective than desoxycorticosterone acetate in reducing urinary sodium and chloride excretion in man.<sup>13</sup> The feebleness of effects of corticosterone and dehydrocorticosterone (IX) on electrolyte excretion are qualitatively like those of desoxycorticosterone, however.<sup>10</sup> It should be mentioned that little experience with esters of corticosterone has been acquired.

Despite its efficiency in maintaining the lives of adrenalectomized animals under the protection of the laboratory, desoxycorticosterone fails when certain specific stresses are placed upon the organism. Among the best understood of these stresses are those that bring out defects in carbohydrate metabolism which are imperfectly realized in the protected state. Several steroids obtained from the adrenal gland and having in common an oxygen atom on carbon 11 will efficiently correct these defects in carbohydrate metabolism. These compounds, corticosterone (VIII), dehydrocorticosterone (IX), 17-hydroxycorticosterone (X), and 17-hydroxy-11-dehydrocorticosterone (X) are commonly identified in this country by letters given them in Kendall's laboratory. In this sequence these are B, A, F, and E. Reichstein's lettering<sup>2</sup> differs and should not be confused with that of Kendall. As judged by isolation procedures which, of course, may err, A and E are most abundant in the gland (340 and 330 mg. per 1000 pounds respectively) while B (180 mg.) and F (less than 100 mg.) are less abundant, according to Kendall.<sup>4</sup> Resembling desoxycorticosterone in the presence of ketones at carbon 3 and carbon 20, a double bond at 4 to 5, and an alcohol group at 21, these four substances all differ from it in the presence of the oxygen at carbon 11. This feature has thus far seemed to be

decisive for influence upon carbohydrate metabolism and to have retarded the synthesis of these steroids.

The steroids influencing carbohydrate metabolism appear to do so by increasing the rate of gluconeogenesis from protein and other precursors when this is necessary and by influencing the rate of disposal of glucose.<sup>7</sup> The relative importance of these two processes varies with experimental conditions. Much is obscure concerning the precise site of action of these substances and the extent to which fat metabolism is involved. In any event the depletion of glycogen stores and appearance of hypoglycemia during fasting in the adrenalectomized animal are prevented, the exquisite sensitivity to insulin is abolished, and phlorhizin and pancreatic diabetes are permitted their conventional evolution. The fatigability of electrically excited muscle in Ingle's test procedure is made more nearly normal in the adrenalectomized rat by the intravenous infusion of glucose or by steroids with an oxygen on carbon 11. In the prevention of vascular collapse induced by intestinal manipulation as described by Swingle and his associates,<sup>14</sup> the favorable effect of 11-oxygen compounds may depend more upon obscure benefits accruing to the intrinsic metabolism of the vascular system than upon the availability of circulating glucose. Similar situations may well exist elsewhere. In none of these instances does desoxycorticosterone seem to repair the defect due to adrenalectomy. In so far as the limited supply of the proper cortical steroids has permitted study in man, the data of Thorn and his associates,<sup>15</sup> using cortical extract, corticosterone, and 17-hydroxy-11-dehydrocorticosterone to correct anomalies of carbohydrate metabolism in Addison's disease, are consonant with work in lower forms. Corticosterone is a relatively weak agent, the effects of 85 mg. being much less clear cut than those of 33 mg. of 17-hydroxy-11-dehydrocorticosterone.

Thorn and Clinton<sup>16</sup> later provided a more complete analysis of the effects of 33 mg. of 17-hydroxy-11-dehydrocorticosterone (compound E) in a patient with both Addison's disease and diabetes mellitus, a patient who interestingly enough could maintain a higher blood sugar level than is customary in adrenalectomized depancreatized animals. Under the influence of compound E the urinary glucose was doubled, while urinary nitrogen, phosphorus, sodium and chloride, and urine volume were increased. Urinary potassium was unaffected. The blood sugar was raised, and the basal metabolic rate somewhat increased, while the nonprotein respiratory quotient was reduced from 0.82 to 0.73. Ketonuria was increased. The increase in protein decomposition as judged by the rise in urinary nitrogen was insufficient to account for more than a small fraction of the glucose excreted, just as in several previous experiments in lower forms.<sup>7, 17</sup> The interpretation offered, in agreement with previous workers, is that glucose consumption relative to that of fat was reduced. The entire problem of the interconversion of glucose

and fat under these circumstances and of the discriminative utilization of these two sources of energy by the body is worthy of further study.

The disposition of certain doses of 17-hydroxy-11-dehydrocorticosterone to increase urinary sodium and chloride excretion as illustrated, is shared by 17-hydroxycorticosterone<sup>18</sup> and differentiates these substances bearing a hydroxyl at carbon 17 from their relatives dehydrocorticosterone and corticosterone, which always induce sodium and chloride retention when given in effective dosage.<sup>10</sup> The renal loss of phosphorus after compound E is attributable to the loss of tissue in the course of gluconeogenesis from protein and has been observed repeatedly in rats,<sup>17</sup> and dogs,<sup>19</sup> with steroids exerting this effect. The absence of potassium diuresis either in a human subject or in dogs,<sup>19</sup> in brief experiments, when such tissue loss prevails, may be due to temporary transfer of potassium to sites of new glycogen deposit. In the experience of Long,<sup>7</sup> in the rat, potassium was lost with phosphorus and nitrogen during gluconeogenesis induced by any adrenal agent. Desoxycorticosterone acetate is devoid of influence on either nitrogen or phosphorus excretion save in recovery from suprarenal insufficiency when material retained in the body during a period of renal failure is discharged.

The induction of atrophy of the normal adrenal cortex may apparently be produced by nearly any of the biologically active adrenal steroids,<sup>20-22</sup> although desoxycorticosterone is less potent than corticosterone or 17-hydroxy-11-dehydrocorticosterone in either regard.<sup>21, 22</sup> The thymus was well preserved in rats receiving 5 mg. of desoxycorticosterone acetate daily for four weeks in one series of experiments.<sup>23</sup> Corticosterone and 17-hydroxy-11-dehydrocorticosterone readily induce thymic atrophy.<sup>21, 22</sup>

The potency and the properties of certain adrenal extracts are not as yet fully accounted for by the pure steroids contained therein. These possibilities exist: (1) Some unknown steroid is present; (2) some known steroid exists in such a form, for example as a conjugate, that its activity is enhanced in some respects and reduced in others; (3) some obscure synergism between two or more known compounds is operative. Potent amorphous fractions have been obtained by several workers. That of Kendall<sup>4</sup> will maintain adrenalectomized dogs in good health with normal blood concentrations of urea and electrolytes in a dosage of 1 to 2 micrograms per kilogram per day. For comparable effects 15 micrograms of desoxycorticosterone acetate per kilogram, 100 micrograms of corticosterone per kilogram, and 10 mg. of compound E per dog are required. Kendall, furthermore, ascribes an especial advantage to this fraction in maintaining renal function as judged by blood urea concentration. The amorphous fraction does not effect carbohydrate metabolism nor induce adrenal and thymic atrophy readily as do the substances with oxygen at carbon 11, nor does it distort the pattern of serum electrolytes when given in large dosage as does desoxy-

corticosterone. An elucidation of its nature is essential for our understanding of adrenal secretions.

Of the remaining 21 carbon atom steroids isolated from the adrenal cortex, 17-hydroxy-desoxycorticosterone possesses some biologic activity analogous to that of desoxycorticosterone, while  $17\beta$  hydroxyprogesterone (XI) is a weak androgen which lacks progestational and typical adrenal cortical functions. Neither, however, has been fully characterized in metabolic studies. Of the 19-carbon atom steroids, adrenosterone (XII), adrostane-3 ( $\beta$ ):11 ( $\beta$ ) diol-17-one, and  $\delta$ -4-androstene:3-17 dione (XIII) are androgens, although not strongly so, and may arise during the working up of the extracts. Great interest attaches to the androgenic compounds in view of the possibility that the normal adrenal cortex of man may have some effects related to those of the androgens and that hyperplastic and neoplastic adrenal cortices certainly do. Powerful androgens such as testosterone have not as yet been obtained from the adrenals. Estrone (V) has been obtained from the adrenal. The significance of this finding is enhanced by the occasional occurrence of estrogen-secreting neoplasms in mice and man.

The biologic effects of large amounts of the various steroids of the adrenal gland will be discussed in conjunction with the interpretation of the manifestations of adrenal cortical tumors. Numerous less well-studied physiologic expressions of adrenal function, such as resistance to cold, to water intoxication, and to thyroxin and cutaneous pigmentation have been omitted from the discussion since it is not yet known that agents different from those described are required for their control.

#### THE NATURE OF THE ADRENAL CORTICAL HORMONES

The disposition to refer to any of a multitude of compounds which are obtained from a gland or which, when synthesized, possess biologic properties resembling those of some internal secretion as a hormone should be recognized for what it is, a convenience which taken too seriously begs an important scientific question. Short of the utopian accomplishment of isolating a humoral agent from the blood stream without impairing its integrity, we lack direct means of ascertaining what is and what is not the actual secretion of a gland. As Houssay<sup>24</sup> has recently emphasized with regard to the pituitary body, even the most thorough and brilliant of chemical analyses of the constituents of a tissue must be supplemented by physiologic analysis. Precision of replacement therapy is necessary for a reliable inference as to what is delivered to the circulation by a gland of internal secretion. The enormity of this task as far as the adrenal cortex is concerned is readily apparent, the biologically active constituents of the gland are numerous and varied, the functions subserved by the gland are complex and widely ramifying. Even a steady determination to seek unity in the midst of

proximity, such as is apparent for example in the thinking of C. N. H. Long<sup>7</sup> or Fuller Albright<sup>25</sup> has its frustrations.

Of the adrenal steroids isolated, corticosterone seems most nearly to fulfill the physiologic requirements imposed upon any agent offered as a prospective sole and single secretion. It possesses both a capacity to sustain the adrenalectomized animal living on a normal supply of salt and a capacity to initiate the necessary modifications of carbohydrate and protein metabolism required by the adrenalectomized animal called upon to endure pertinent metabolic stress. That it is less effective than desoxycorticosterone in the former regard and than 17-hydroxy-11-dehydrocorticosterone in the latter may not be decisive. Greater potency may possibly be obtained from thus far unstudied esters, illustrated by the superiority of desoxycorticosterone acetate to desoxycorticosterone, and the type of conjugate provided by the gland itself may be expected to have advantages. There is no reason to believe that corticosterone could ever be androgenic. This limitation probably exists, however, for any and every agent serving to repair suprarenal insufficiency and lends significance to anatomic studies seeking to implicate special cell types in androgen secretion.

The most important physiologic evidence casting doubt on corticosterone as the sole secretion with typical adrenal properties seems to lie in the work of Lewis and his associates.<sup>19</sup> The urinary excretion of sodium and chloride as well as of nitrogen and phosphorus was increased in the normal dog exposed to anoxia as compared to the adrenalectomized dog. Such accompaniments of gluconeogenesis evoked by this procedure are unlike any known effects of corticosterone and suggest the direct participation of a compound like 17-hydroxy-11-dehydrocorticosterone in the process to effect sodium and chloride loss. On the other hand these very properties of 17-hydroxyl compounds would seem to unfit them as agents for conserving body salt. In this connection, however, the experience of Kendall in maintaining adrenalectomized dogs with 10 mg. of compound E daily, and of Kuizenga and Cartland,<sup>26</sup> in maintaining adrenalectomized rats with compound E, demonstrates that dosages of the 17-hydroxyl compounds may be found which are not inimical to the maintenance of salt and water balance.

It will be of great interest to examine the new pure pituitary adrenotropic principle<sup>27-30</sup> for its effect on salt and water metabolism. As thus far studied this agent evokes a gluconeogenic, thymus-depressing, adrenal secretion, which antagonizes insulin and whose catabolic properties oppose the effects of the growth hormone of the pituitary body.<sup>31</sup> These are the responses expected of potent adrenal steroids bearing an oxygen on carbon 11. It is problematical whether such an adrenal hormone evoked by such an adrenotropin could efficiently conserve body salt in the manner of desoxycorticosterone or corticosterone. It should furthermore be noted that the most efficient agent in maintaining life

of the protected adrenalectomized dog, the amorphous fraction, is without effect upon carbohydrate metabolism even in the heaviest dosage.

It may be concluded as likely but not established beyond cavil that the various demands placed upon the adrenal cortex in the ordinary course of its life have been best served by the secretion of at least two hormones, one conserving salt and water and the other effecting efficient mobilization and utilization of carbohydrate. The provision of androgens and estrogens, somewhat special and poorly understood functions, not known to be of material importance to the maintenance of general well-being, requires separate, differentiated secretions, whether they be delivered from cells of recognizably different structure or not. The place of all of these in the physiologic expressions of adrenal neoplasms will be sought.

#### CLASSIFICATION OF THE SYNDROMES DUE TO ADRENAL CORTICAL TUMORS

All students of adrenal cortical tumors have been impressed by the variety of their manifestations. The clinical aspects are dealt with fully in Cahill's article of this series and will be briefly considered here only in so far as the association of particular symptoms and signs creates assumptions in regard to common pathogenesis. Taken in rough form and allowing freely for intergrades, I believe the following types would be acceptable to most workers:

1. Adrenogenital, occurring in children of either sex but more frequently in girls and occasionally in adult women. The masculinization is intense with precocious or heterosexual growth of the phallus, maturation of a masculine larynx, proliferation of body hair of masculine distribution, temporarily enhanced somatic growth in children and pronounced development of the musculature. Amenorrhea is usual in the female, and breast growth is usually held in abeyance. Similar expressions of adrenal hyperplasia in the young of either sex occur.

2. Cushing's syndrome, occurring in women and children. The masculinization is less intense than in the adrenogenital syndrome and is represented chiefly by hirsutism. Systemic disturbances including adiposity of the "buffalo type," plethoric appearance with the "moon face," hypertension, purple cutaneous striae, ecchymoses, osteoporosis and diabetes are frequent. Amenorrhea is the rule. Similar expressions are given by adrenal hyperplasia, thymic tumors with adrenal hyperplasia, and pituitary tumors with or without adrenal hyperplasia. A somewhat modified form, with loss rather than increase in body hair and with testicular atrophy, occurs rather rarely in men with pituitary tumors but has occurred only twice as an expression of adrenal tumors. Crooke's hyalinization of the basophiles of the pituitary body is characteristic of this type of disorder, irrespective of the tumor found.

3. Intergrades between Types 1 and 2, expressed for example by the



occurrence of obesity, hypertension, cutaneous striae and glycosuria, individually or together, in those in whom masculinization is intense.

4. Isolated expressions of the neoplasm, illustrated by the case of Sprague and his associates in which diabetes mellitus was the sole sign of the disease. Kepler and Keating<sup>32</sup> cite an instance in which amenorrhea was the sole endocrine stigma.

5. Feminization, a rare manifestation in men, characterized by atrophy of the testes, loss of body hair, and growth of the breasts. Unknown in the young boy it is expressed in larval form, complicated by other signs and symptoms, in a few cases in girls in which menstruation and breast development are precocious.

6. Tumors without endocrine manifestations.

The importance of distinguishing between the adrenogenital and Cushing's type was stressed by Haymaker and Anderson<sup>33</sup> in their excellent review of the subject and was given a metabolic emphasis by Albright and his associates,<sup>25</sup> who suggested that the disturbances in protein metabolism were largely anabolic in the first type and catabolic in the second. Cahill and associates,<sup>71</sup> accepting this same essential distinction from the strictly clinical standpoint, emphasized that contralateral adrenal atrophy was rare in the more virilistic form and common in the Cushing's form. Thompson and Eisenhardt<sup>35</sup> have pointed out that prior to 1940, the termination of their series, all eighteen patients with the typical Cushing syndrome, in which adrenal tumors were removed, died. Successful resection had been possible only in subjects with other expressions of adrenal hyperfunction. These authors also note that the Crooke changes were quite consistently found in the pituitaries of individuals with the fully evolved Cushing type of disorder but were absent in those integrades in which diabetes, hypertension, and virilization coexisted. The thorough review of Kepler and Keating<sup>32</sup> gives especial attention to the atypical cases reported. It seems to me that while a good deal is to be gained by classifying the signs and symptoms somewhat in this manner, that rigidity is to be avoided. Neither the clinical facts nor our knowledge of pathogenesis warrant sharp and inveterate distinctions between categories.

In the following account the more important symptoms and signs of adrenal tumors are considered individually and an attempt made to account for them in terms of the properties of adrenal secretions and their relatives.

#### HYPERTENSION

Sustained hypertension, often severe, is commonly found in the victims of adrenal cortical tumors. Among the most spectacular of numerous reports is the 11-month-old girl, reported by Marks, Thomas, and Warkany,<sup>36</sup> whose blood pressure was 245/145 mm. Hg. Renal defects sufficient to account for the hypertension have not been consistently found. In some subjects arteriolosclerotic lesions, even approaching

those of malignant nephrosclerosis, have been found in the kidneys at autopsy. In others no conspicuous defects were present. Very little data based upon the more elaborate and precise modern methods of measuring renal function are available.

Recent experience with desoxycorticosterone acetate in Addison's disease has provided us with our first clue as to the nature of the adrenal steroids responsible for this remarkable hypertension. Numerous physicians<sup>11, 12, 37-39</sup> using especially the heavy dosage of desoxycorticosterone acetate prevailing on the introduction of the substance observed that elevations of the blood pressure to 150 to 170 systolic, 90 to 110 diastolic were by no means uncommon. Thorn, Dorrance, and Day<sup>12</sup> found that 34 per cent of their sixty-four patients had a systolic blood pressure above 150, a diastolic above 100, or both at some time in the course of treatment. A value as high as 212/116 was observed by McCullagh and Ryan<sup>38</sup> in a man receiving 10 mg. of desoxycorticosterone acetate daily together with 10 Gm. of added salt. This hypertension occurs irregularly and may be transient. It may appear only after several weeks to months of treatment and may or may not be accompanied by gross edema. Thorn and Firor<sup>39</sup> thought that reduction of salt intake without altering the dose of the steroid would reduce the blood pressure and Loeb<sup>40</sup> recorded a similar experience in which salt alone produced hypertension, but these points have hardly been sufficiently well documented in an adequate number of patients as yet. Pre-existing hypertension may well be responsible in certain instances, but the experiments of Swingle and his associates<sup>41</sup> demonstrate that this is not necessary. Production of hypertension in normal individuals by this steroid has not been attempted.

Reported first by Kuhlmann and his associates,<sup>42</sup> induction of hypertension in dogs by desoxycorticosterone acetate has been studied in further detail by Swingle, Parkins, and Remington.<sup>41</sup> Adrenalectomized dogs in their experience, receiving 2 mg. of the steroid per day (eight to sixteen times the maintenance dose), showed an elevation of systolic blood pressure that began in forty-eight hours and continued for six to thirteen days at which time it stabilized in the neighborhood of 130 to 140 mm. of Hg, 20 to 30 mm. above normal levels. On cessation of excessive treatment the blood pressure slowly declined to normal within seven to ten days. One normal dog receiving the same treatment showed only a slight transient response. The plasma volume of the adrenalectomized dogs increased 30 to 40 per cent within three to seven days and then receded to slightly above the base line despite continued treatment. This together with the occasional complete dissociation between increased plasma volume and increased blood pressure led Swingle and his associates to discount any cause and effect relationship between the two.

Grollman, Harrison, and Williams<sup>43</sup> noted the production of an elevation of 40 mm. of Hg in rats receiving 0.5 mg. of desoxycorticosterone

acetate daily. This effect was prevented by the oral administration of a renal extract effective in reducing the blood pressure of rats with hypertension due to partial nephrectomy. The hypertensive influence of the steroid was held accordingly to involve a renal mechanism. Similar elevations in blood pressure in the rat were obtained with estradiol benzoate, stilbestrol, progesterone, and testosterone. The dosages used were enormous. No influence on the blood pressure of man with maximum therapeutic doses of these substances has been observed.

It can readily be seen from the foregoing that a beginning has been made in the study of the hypertensive effects of the steroids. Desoxycorticosterone is by no means the only one worthy of consideration. Although large amounts of adrenal extracts have not proved hypertensive, Swingle and his associates point out that such extracts share with desoxycorticosterone the power of protecting the adrenalectomized animal against the circulatory collapse and edema induced by transfusions of serum. The same group<sup>14</sup> later established that 17-hydroxy-11-dehydrocorticosterone was much more effective than desoxycorticosterone in protecting the adrenalectomized dog against collapse following manipulation of the intestines. It does not follow, of course, that such an agent in large amounts would be hypertensive but the matter is worth suitable inquiry.

#### SALT AND WATER METABOLISM

The swelling of the soft tissues of the face and eyes of certain patients with adrenal tumors may be in part due to salt and water retention in those tissues, and edema elsewhere may be due to hormonal influences on salt and water metabolism as well as to cardiac insufficiency. Polyuria and polydipsia not accounted for by glycosuria have been experienced by patients with the Cushing type of disorder. Complete and acceptable salt and water balance studies are not available. More attention has been paid to the concentration of serum electrolytes, chiefly in the victims of Cushing's syndrome not due to adrenal tumor, but it is well established that such changes in concentration often reflect disturbances in balance only sluggishly and hence do not substitute for exacting metabolic study.

In 1933 and 1934, Kepler and his associates<sup>44, 45</sup> called attention to the fact that occasional individuals with Cushing's syndrome showed a reduction in the concentration of chloride and potassium in the serum and an increase in bicarbonate. The 44-year-old woman reported by McQuarrie, Johnson, and Ziegler,<sup>46</sup> with Cushing's syndrome, showing slightly enlarged adrenals and Crooke's changes in the pituitary, illustrates these phenomena. Her serum bicarbonate was 38 meq. per liter; Cl, 89 meq. per liter; Na, 156 meq. per liter; K, 3.0 meq. per liter. The pH ranged from 7.55 to 7.60. An undetermined acidic fraction was present. Potassium chloride administration increased the

serum potassium and chloride and reduced the bicarbonate somewhat. Willson, Power, and Kepler<sup>47</sup> studied a man 39 years of age, with Cushing's syndrome, in whom operation disclosed no adrenal tumor. His serum Na of 137 meq. per liter was normal but his serum K was reduced to 2.2 meq., Cl to 78, and the bicarbonate was increased to 46 meq. per liter. Administration of 8 Gm. of potassium chloride per day (56 Gm. all told) yielded 26 Gm. to the body, of which only 2 Gm. could be assigned to extracellular fluids. This was interpreted as meaning previous exhaustion of potassium stores. Anderson, Haymaker, and Joseph<sup>48</sup> reported evidence suggesting increased urinary loss of potassium and retention of sodium in patients with Cushing's syndrome of unknown origin and Haymaker and Anderson<sup>49</sup> reported symptomatic improvement in patients receiving potassium citrate. The patient of Willson and his associates did not improve, however, despite correction of the anomalies in concentration of electrolytes. Kepler has on several occasions stressed the infrequency of alterations of serum electrolytes in Cushing's syndrome. In adrenal cortical tumors the only evidence of such changes that I know of is the level of 160 meq. of Na without alteration of K noted by Howard and Whitehead<sup>49</sup> in a patient with essentially virilistic manifestations and the data recorded in Table I,

TABLE I

CONCENTRATION OF SEVERAL SERUM CONSTITUENTS IN A 40-YEAR-OLD WOMAN SUFFERING FROM A PROVED MALIGNANT ADRENAL CORTICAL TUMOR\*

DATE	CO <sub>2</sub> (MM. PER LITER)	Na (MM. PER LITER)	Cl (MM. PER LITER)	K (MM. PER LITER)	PH
1/22	39.1	147.2	93.1	5.5	7.52
1/30	40.2	152.6	90.4	3.14	7.53

\*Courtesy of Dr. A. S. Alving.

secured by Dr. A. S. Alving, in a woman with Cushing's syndrome due to a malignant tumor of the adrenal cortex. These latter changes are essentially the same as those previously recorded in patients in which this syndrome occurred in the absence of adrenal tumors.

Progress toward explanation of the distorted electrolyte patterns seen in hyperadrenal states is now being made on the basis of our knowledge of the properties of large amounts of adrenal steroids. All writers on the subject have appreciated a possible analogy with the effects of desoxycorticosterone acetate. This substance induces retention of sodium, chloride, and water and impels renal excretion of potassium in the adrenalectomized dog and in Addison's disease in man. These effects are likewise seen at least temporarily in the normal of both species. The consequences of more protracted treatment with large amounts of desoxycorticosterone have been studied with care by Loeb, Ferrebee, and their associates in the normal dog<sup>50, 51</sup> and are complex. Prodigious thirst and ensuing polyuria supervene, apparently excited

## CARBOHYDRATE AND PROTEIN METABOLISM

It has long been known that diabetes mellitus occurs frequently among the symptoms of adrenal cortical tumors and that it occurs in those with Cushing's syndrome in whom no such tumor can be found. Lukens, Flippen, and Thigpen<sup>63</sup> record impaired glucose tolerance in one-half of fifty-five reported cases of adrenal carcinoma, adenoma, or bilateral hyperplasia. Glycosuria was considerable in nineteen. Such glycosuria may be abolished by dietary restrictions,<sup>64</sup> or may require relatively large doses of insulin, up to 145 units a day.<sup>65</sup> Even when the diabetes is mild, insulin may have less effect than would be expected when given in conjunction with glucose,<sup>66</sup> but in other instances there seems to be nothing unusual about the amounts of insulin required to control glycosuria.<sup>67</sup> Diabetes is usually associated with hirsutism, hypertension, amenorrhea, and obesity and frequently with a dusky skin and colored cutaneous striae<sup>64</sup> but may, as in the remarkable case of Sprague and his associates, represent the sole endocrine expression of the tumor.<sup>65</sup> It is apparently rare in those instances of adrenal hyperplasia or neoplasia in girls or young women in which vigorous masculinization is the predominating feature of the illness. Visible lesions of the pancreas do not seem to account for the diabetes,<sup>63</sup> but it is difficult to eliminate the predisposing force of latent diabetes mellitus in the ordinary sense.<sup>32, 64</sup> An elevation of the basal metabolic rate is frequently but by no means always associated with the diabetes.<sup>64</sup> If increased thyroid secretion is responsible for such elevation, the familiar influences of hyperthyroidism in impairing glucose tolerance may well be contributory.

Woodyatt<sup>68</sup> observed that in a man with Cushing's syndrome of unestablished etiology, but improved by x-ray therapy to the pituitary body, the urinary urea excretion was exceptionally high even when the glycosuria was controlled by insulin. On a diet adequate in calories and containing 81 Gm. of protein, 20 to 24 Gm. of nitrogen (equivalent to 125 to 150 Gm. of protein) were found daily in the urine. Balance could eventually be achieved by increasing the protein intake. Woodyatt suggested that the polyuria, up to 6,700 c.c. daily, might be accounted for by the high rate of nitrogen excretion. These observations were fully confirmed when the patient went to Boston under the care of Cushing. At this time the protein in the diet had to be increased to as much as 475 Gm. per day to maintain balance.

The discovery of the disposition of adrenal extracts and especially of adrenal steroids with an oxygen at carbon 11 to favor the mobilization of glucose and to restrict its disposal led to a rational theory of the mechanism of diabetes mellitus induced by adrenal tumors. Lukens and his associates<sup>63</sup> and C. N. H. Long introduced this view. While at first glycosuria was induced by adrenal agents only in the depancreatized animal, Ingle<sup>69</sup> has recently succeeded in producing severe

glycosuria in intact rats fed a high carbohydrate diet with large amounts of 17-hydroxy-11-dehydrocorticosterone. Urinary nitrogen increased also, but not sufficiently to account for the glucose excreted. In other experiments as previously mentioned, such a loss of nitrogen during gluconeogenesis was accompanied by discharge of phosphorus and under some circumstances at least by potassium.<sup>7</sup> Such catabolic effects presumably operate in the inhibition of somatic growth of normal young rats induced by heavy dosages of 11-oxygenated steroids,<sup>22</sup> although glycosuria was not recorded as occurring in these particular animals. Under other circumstances, however, as in the depancreatized dog described by Kendall,<sup>1</sup> glycosuria was enhanced by compound B without increasing urinary nitrogen excretion. It may be fairly said that it is not as yet entirely clear as to when the gluconeogenic process will predominate in the response to these steroids and when other events, now usually interpreted as meaning restricted glucose consumption, are of most importance. It may well be that the heavier the dose of the steroid, the more decisive is the role of gluconeogenesis. The capacity of the pancreas to secrete insulin may be expected to determine the extent of the opposition to such processes, at least in part. A basis for an understanding of the diabetes and occasional severe nitrogen loss in terms of the excessive action of known adrenal steroids is thus seen to be established, although many details require elucidation.

With the frequency of diabetes in Cushing's syndrome in mind and supported by the observation of Woodyatt on urinary nitrogen losses, and by the demonstration of the catabolic effects of several adrenal steroids, Albright and his associates<sup>25</sup> have formulated a bold general theory of the pathogenesis of the signs of Cushing's syndrome. No attempt was made to account for the hypertension. The predominately anabolic phenomena in those subjects with intense masculinization were explicitly excluded.

By protein wastage in the course of gluconeogenesis, Albright seeks to account for:

1. The wasting of muscle with consequent weakness
2. The thinning of the integument with the appearance of striae and rubor
3. The simulation of obesity by the loss of effective muscular and cutaneous support.
4. The loss of bone matrix with consequent osteoporosis
5. The thinning of arteriolar and venous walls with resulting fragility and hemorrhage

Albright and his associates suggested that testosterone by virtue of its anabolic effects might serve to counteract and repair the damage wrought by such tissue protein dissolution. They succeeded in inducing nitrogen and phosphorous retention in these subjects with testosterone

propionate in much the same manner as had previously been observed in eunuchoids<sup>58, 70</sup> and in normal men and women.<sup>55, 70</sup> They furthermore demonstrated a remarkable delayed retention of calcium that had not heretofore been observed with the androgen. The improvement of their patients increased their confidence in the soundness of their views.

The stark simplicity of this comprehensive theory may not survive. Albright<sup>71</sup> has already attempted to adapt it to new facts. It has not been possible as yet to demonstrate that the extraordinary nitrogen deficits observed by Woodyatt are of general and frequent occurrence. In none of the nitrogen balances recorded by Albright and his associates<sup>25, 72</sup> in Cushing's syndrome has any such nitrogen loss been found, nor was it apparent in the briefer studies of Willson<sup>47</sup> or Paschkis<sup>67</sup> and their respective co-workers. Indeed, Albright found that one such patient could conserve nitrogen as well or better than normal subjects when placed on a low protein diet.<sup>72</sup> The possibility remains that nitrogen deficits had occurred in the past in these subjects and that the protein stores were so depleted that there was little more readily mobilizable nitrogen to dissipate. Only further metabolic studies at all stages of the disease can settle this point. I am inclined to feel that such nitrogen losses as Woodyatt obtained must be due to relatively intense stimulation of gluconeogenesis by large amounts of steroids with an oxygen at carbon 11, and that losses of protein from the body as a whole of sufficient magnitude to be detected in metabolic experiments are rare and may not be of general significance. Albright has attempted to surmount the difficulty by altering his concept of the action of the adrenal steroids from catabolic to antianabolic.<sup>71</sup> I am not yet clear as to the advantages accruing from this change in emphasis. Certainly specific tissues such as bone suffer destruction in Cushing's syndrome. The heart of the matter seems to lie in whether such phenomena can be conceived simply as an exaggeration of the normal effects of the carbon 11 oxygen-bearing steroids on the protein metabolism of these tissues. In suggesting this interpretation, Albright and his associates have provided our thinking with an important challenge although the complexities and uncertainties of the data now available render the ultimate fate of this hypothesis obscure.

It is known that some tumors of the adrenal cortex in the child induce unusual somatic growth for a time with rapid development of the musculature. These especially in the boy may lead to the "*infant hercules*" type or the "*burly brewer's drayman*." Considerable hypertrophy of the phallus, deepening of the voice, and growth of hair of masculine distribution usually accompany the excessive somatic growth. Neither corticosterone, its relatives with an oxygen at carbon 11, nor desoxycorticosterone possess androgenic properties sufficient to accomplish such transformations of the body, nor do they induce the re-

tention of nitrogen and phosphorus necessary for growth. Testosterone propionate and methyl testosterone, however, have been shown to produce metabolic responses compatible with tissue growth in the child, and in the normal and sexually underdeveloped man and woman.<sup>58, 70, 72-75</sup> Retention of nitrogen, inorganic phosphorus, sulfate, and potassium have been induced. Sodium and chloride retention do occur at least in the first phase of treatment, as with desoxycorticosterone and corticosterone, but expansion of the extracellular fluid compartments of the body do not, as a rule, seem excessive in long-term experiments. Calcium retention has been observed only in special circumstances,<sup>71</sup> but it seems likely to me that it too is a general reaction which will be clearly established when suitable experiments are carried out. Most of these influences may be exerted by as little as 5 mg. of testosterone propionate daily,<sup>74, 75</sup> amounts that are scarcely androgenic, so that the body is relatively sensitive to the anabolic effects of these steroids. Recently, numerous workers have demonstrated that actual growth in height and weight of undergrown, underdeveloped children may be produced by testosterone propionate,<sup>76-78</sup> methyltestosterone,<sup>73, 79</sup> and in boys by the testicular secretion as evoked by chorionic gonadotropin.<sup>78, 80</sup> It is thus possible now to account for the unusual somatic growth and superlative muscular development of boys with testicular tumors by the excessive delivery of androgenic hormones from the neoplastic testes. The somewhat similar clinical status of certain victims of adrenal hyperplasia and neoplasia suggests that the adrenal cortex secretes substances with similar androgenic and anabolic propensities at least under these circumstances. What this substance may be is unknown. The several androgens isolated from the adrenal cortex are not powerful and have not been tested for metabolic effect. Testosterone is not as yet known as an adrenal constituent. Although progesterone has been isolated from the adrenal cortex and has somewhat feeble androgenic properties in some species, its androgenic and metabolic effects as thus far known in man seem rather too indistinct to suggest any important role for this substance in the metabolic or androgenic expressions of adrenal tumors.

Masculinization in one form or another is a common part of the symptomatology of the adult female with adrenal tumors even though it is usually less extreme than in the child. Any metabolic action of the androgen secreted might be expected to oppose the nitrogen, phosphorus, sodium, chloride, potassium, and water-expelling forces of some steroids present in excess and to reinforce any sodium, chloride, potassium, and water-retaining forces of other steroids. Thus a further factor is introduced into the clinical melange. Difficulties experienced in accounting for the metabolic expressions of adrenal tumors in terms of the effects of the more typical adrenal steroids may hence be expected.

It should be mentioned briefly that the anabolic effects described here for the androgens are not inextricably bound with androgenicity in the



strict sense. Estradiol benzoate in large doses has certain anabolic effects resembling those of the androgens<sup>55</sup> and depression of estrogen secretion has been implicated in postmenopausal osteoporosis in man.<sup>61</sup> Several workers<sup>71, 82</sup> have speculated on the possibility that the normal adrenal might secrete some steroid with anabolic properties, which follows a metabolic path like that of testosterone in the body and yields in the urine such derivatives as androsterone and etiocholan-ol-one. The existence of such a substance and its role in the economy of the organism either in health or disease remain uncertain.

The reports of Wilkins, Fleischmann, and Howard<sup>65</sup> and Butler, Ross, and Talbot<sup>84</sup> describe the development of suprarenal insufficiency in children suffering from adrenal hyperplasia that expressed itself by unusual body growth and exceptional maturation of masculine secondary sex characters. The proliferating cortical cells were histologically unlike those of the normal adrenal and had displaced normal cortical tissue.<sup>83</sup> We thus have evidence for a specialized adrenal cell capable of secreting androgens and incapable of secreting typical adrenal hormones, evidence which, by the way, was never satisfactory to me in previous discussions of the "androgenic zone" of the human fetal cortex. Further illustration is provided that androgens will not effectively repair suprarenal insufficiency. Clearly one must consider not only what a neoplasm can do by secreting certain hormones in excess but what the viable normal residue can do. Some such considerations may help to clarify the obscure cases of collapse in newborn infants with hyperplastic adrenal cortices reviewed by Kepler and Keating<sup>32</sup> and may even be required in the study of the pathogenesis of the symptoms of other adrenal tumors.

#### BONES AND CALCIUM METABOLISM

The affected bones in Cushing's syndrome are atrophic with little evidence of cyst formation or of the osteoclastic reaction so common in hyperparathyroidism. Osteoid tissue bespeaking an especial difficulty in calcification has not been described, to my knowledge. Serum levels of calcium are normal, as a rule, while those of inorganic phosphorus may be low. Hypertrophy of the parathyroid glands is not a common autopsy finding although it has been observed.<sup>33</sup> In the patient reported by Freyberg and his associates,<sup>85, 86</sup> a boy with pituitary adenoma and extreme osteoporosis but curiously enough with atrophic adrenals, neither the striking hypercalciuria nor hyperphosphaturia characteristic of hyperparathyroidism could be found. In Aub's study<sup>87</sup> of one of Cushing's early cases, however, the urinary calcium was some four times the average normal on a low calcium diet, while the fecal calcium approached normal. Hypercalciuria under similar circumstances was recorded by Paschakis and his associates.<sup>67</sup> The calcium balance was not negative to any extent in the subjects of Albright and associates.<sup>25</sup> It

must be confessed that complete balance studies during known active phases of bone dissolution are few and that little data are available in subjects in which adrenal tumors are responsible. Certainly little evidence that hyperparathyroidism is a frequent factor has been adduced.

In the last section, Albright's view that the essential bone lesion lies in loss of protein matrix was discussed. A somewhat similar explanation was offered by the Boston group for the osteoporosis that may occur after the menopause in women.<sup>81</sup> In this latter instance estradiol benzoate induced retention of calcium and phosphorus although the technically difficult demonstration of bone repair has as yet not been accomplished. In Cushing's syndrome, although an estrogen deficit must often be present, estradiol benzoate did not produce a strongly positive calcium balance<sup>85</sup> and the osteoporosis of the patient reported by Paschkis and associates,<sup>87</sup> progressed during treatment with stilbestrol. The extent to which the damaged bone can be repaired by testosterone remains to be seen, although the positive calcium balance described by Albright and his associates during treatment with the androgen is encouraging. This influence is not specific for Cushing's syndrome as it has been seen in aged men with osteoporosis<sup>88</sup> and may be at least in some degree a general reaction to the androgen. Freyberg and Grant<sup>86</sup> had difficulty in increasing calcium absorption by increasing dietary calcium or by giving vitamin D, although injected calcium was well retained. This type of observation has not been extended. Experimental work in the effects of various adrenal steroids on the bones of animals together with controlled metabolic observations are clearly necessary for the proper understanding of the osteoporotic process.

The growth of the long bones and the trunk in the early phase of the adrenogenital syndrome is in all probability ascribable to the anabolic activities of the androgens. As mentioned previously, growth in height and increase in bone maturation have now been repeatedly induced in undergrown, underdeveloped children with several androgens. Similarly, the early closure of the epiphysis in these young people may be ascribed to the effects of the androgens, although experimental evidence in man is not as completed in this respect as one might wish.

#### CHANGES IN THE SKIN AND BLOOD VESSELS

Although rubor, purplish cutaneous striae, and a disposition to hemorrhage from superficial skin vessels are among the cardinal expressions of adrenal tumors, we lack convincing explanations for their occurrence. The evidence from infrared photography as to the thinness of the integument is of interest.<sup>25</sup> The extent that loss of protein from the skin and vessel walls either in the course of gluconeogenesis or otherwise is responsible remains uncertain although Albright's provocative

theory that this is decisive is worthy of attention. Protein loss in the course of other wasting disease does not give rubor and hemorrhage from small blood vessels and purple striae, but such protein loss may be controlled still by intact adrenals and hence differ from that induced by an adrenal cortex secreting without restraining influence. Thus, any hypothesis advanced requires further presuppositions for its support and has value chiefly in directing attention to the processes it would explain. Even detailed pathologic study of the affected tissues is now lacking.

The seborrhea and acne frequently seen are perhaps best ascribed to androgens or to some obscure relatives thereof. Androgens alone among hormonal agents are known to increase the activities of sebaceous glands.

#### THE GENITAL DYSTROPHIES

Masculinization due to adrenal tumors may be represented by little more than hirsutism, as in Cushing's syndrome, or may be a veritable inversion of the female organism with hirsutism, hypertrophy of the larynx, growth of the phallus, and maturation of masculine musculature. These latter features are often more conspicuous in children. In boys, precocious evolution of secondary sex characters may occur but tumors enhancing masculine attributes of adult men are excessively rare. All of these reactions, at least in incipient form, have now been produced in man by single androgens such as testosterone or methyl testosterone, and in the immature male by testicular secretions under the influence of chorionic gonadotropin. Steroids with typical adrenal properties are not materially androgenic, and progesterone, which will repair suprarenal insufficiency in some species and is faintly androgenic in some respects, seems hardly capable of such effects in man as far as is now known. Several androgenic steroids as previously described have been isolated from the adrenal cortex, but they are less potent than testosterone in biologic tests and their activity in man has not been examined. Nevertheless, if androstenedione or 17-hydroxy-progesterone were discharged in large amounts by a tumor, something in the direction of masculinization would be expected. Another weak androgen, dehydroisoandrosterone, has been isolated in large amounts from the urine of patients with adrenal tumors and may conceivably contribute to masculinization. It has not itself been obtained from the adrenal and if it is derived from some other steroid, its mother substance is undetermined. At present it must be granted that the actual androgenic adrenal secretion is unknown.

Testosterone in large amounts is inimical to the normal functioning of the ovary.<sup>89, 90</sup> Thus in the detailed studies of Geist and his associates<sup>89</sup> amounts exceeding 500 mg. per month will induce amenorrhea in adult women. On the basis of a large body of experimental work largely in lower forms, this interference is interpretable as due to inhibition

of the release of gonadotropic, follicle-stimulating secretions from the pituitary body. Direct interference with the peripheral effects of the estrogens, as on the vaginal mucosa of women<sup>31</sup> is in all probability involved as well. By either mechanism or both, the circulation of any large amount of androgens with such properties may be expected to militate against the normal evolution and maintenance of certain feminine attributes. This may well be responsible for the deficiencies in normal sex characters of girls and women suffering from adrenal tumors. In some cases, however, amenorrhea may occur without especially conspicuous masculinization. Consideration of such problems must be waived until the responsible adrenal androgens or their close chemical relatives are identified and examined for their influences upon the gonads. A further confusion is exemplified by the fact that some young boys with precocious development of secondary sex characters have shown premature spermatogenesis.<sup>32</sup> This is difficult to explain. Large amounts of androgens in man depress spermatogenesis<sup>32</sup> although obviously physiologic amounts do not. In several species androgens like testosterone, in certain doses under certain conditions, will sustain or induce sperm production. No such influence is known in man although the matter can hardly be said to have been thoroughly explored. This difficulty is cited to illustrate once more the obstacles met by too facile theoretical disposal of the signs of adrenal tumors.

Much speculation has surrounded attempts to seek an androgenic function for the adrenal in the course of its normal existence and to implicate special cell types in the secretion of such androgens. If such speculations can in the end be brought to firm earth, masculinization by adrenal tumors will become less difficult to understand. Mere exaggeration of a normal function will more nearly suffice as an explanation. Otherwise neoplastic rejuvenation of heterotopic gonadal remnants or the secretion of some perverted metabolite must be invoked. Space cannot be given here for an extended discussion of this problem. Under some circumstances, as in the young male mouse, the adrenal does seem to serve as a vicarious androgen producer in the absence of the testis during a limited part of the life cycle.<sup>93, 95</sup> In the rat certain pituitary gonadotropins will evoke androgen production by the adrenal.<sup>94</sup> In the mouse a specialized juxtamedullary cortical zone (X zone) is present in infancy and involutes under the influence of the testis or of pregnancy.<sup>95, 96</sup> Analogies between this zone and certain juxtamedullary cells of the adult human suprarenal cortex, and more especially of the human fetal cortex, have been sought largely on cytologic grounds. Production of androgens by this zone in the fetus has been hypothesized and the term "androgenic" applied to it.<sup>97</sup> No substantial evidence as to the function of the fetal adrenal cortex has, however, been provided. Goldzieher's more recent view that it serves to secrete a gluconeogenic agent enabling the fetus to endure relative anoxia is as

satisfactory as any involving androgenic functions. Special staining methods led Vines<sup>90</sup> to suggest that fuchsinophilic granules were present in the cells of masculinizing adrenal tumors, or in the cells of hypertrophic adrenals, and not in normal postnatal adrenals. Goormatigh<sup>100</sup> emphasized that masculinizing tumors in his experience contained fuchsinophilic and siderophilic granules not present in indifferent or feminizing tumors and like juxtamedullary cells. A more recent account of the tumors or hyperplasias<sup>53</sup> giving rise both to androgenic phenomena and to suprarenal insufficiency cite histologic differences between the proliferating adrenal cells found and normal adrenal tissue, and provide material evidence that the androgen-secreting cells are incapable of forming the normal adrenal hormones. The relationships between such cells and those of the large zona reticularis of the fetal cortex do not, however, appear to be fully established.

The same general problem has been approached from a different angle. As will appear in a subsequent section, the urine of a castrate man or woman contains androsterone and etiocholan-ol-one, both of which have been identified as breakdown products of injected testosterone. In the castrate these substances presumably arise from some adrenal precursor which takes a metabolic course like testosterone in the organism. Androstenedione which has been isolated from adrenal extracts, for example, could do so. This precursor could be androgenic in its physiologic effects or possess anabolic properties resembling those of the androgens. Several, including the author, have entertained this possibility.<sup>59, 71, 82</sup> Albright and his associates<sup>135</sup> as well as Kepler<sup>139</sup> have sought to implicate adrenal androgens in the maintenance of axillary and pubic hair, especially in women, and the former group have stressed the possible importance of androgen deficits in limiting the growth of short women with primary ovarian insufficiency described by Varney<sup>140</sup> and Albright<sup>135</sup> and their respective associates. It may be concluded that while the normal human adrenal cortex may secrete substances which are active as physiologic androgens, that it has not as yet been incontrovertibly proved to do so. The androgenic urinary derivatives are excreted as biologically inactive conjugates. Their presence does not establish that either they or their precursors behave as physiologic androgens in the organism. Physiologic evidence must be sought and although promising, such evidence is still incomplete.

The situation with regard to the rare feminizing tumors seen in adult men is much the same as in the androgenic tumors. The growth of the breasts and the atrophy of the testis are in accord with the known effects of the estrogens in the male, and large amounts of estrogenic substances have been found in the urine of one such patient.<sup>136</sup> Estrone has been extracted from the adrenal cortex. Adrenal tumors arising in mice ovariectomized shortly after birth evoke intense estrogenic effects in their hosts.<sup>101</sup> Although it is well known that estrogens can be

found in the urine of castrated men or women, their function in the organism is obscure. Such estrogens may come from the adrenal cortex, but to what purpose is unknown. The recent demonstration by Shorr and his associates<sup>102</sup> that estrogens unlike androgens increase the urinary excretion of citrate and hence serve to protect the urinary tract from deposition of insoluble calcium salts and the work of Albright and his associates<sup>81</sup> implicating estrogens in the maintenance of bone emphasize the advances to be expected when attention is paid to the widely ramifying influences of the sex hormones. The extent to which estrogens residual after castration serve such or other nongenital functions is unknown although it seems to me that inquiry along these lines might be useful. It may be expected that when estrogens are circulating in large amounts in those with adrenal tumors that their metabolic as well as their genital effects may enter into the expressions of the disorder. Knowlton and her associates<sup>75</sup> have recently summarized these metabolic effects as far as man is concerned and presented additional data. In addition to favoring increased citrate excretion, as already mentioned, retention of sodium, chloride, nitrogen phosphorus, and, at least under some circumstances, calcium has been induced, by estradiol benzoate. Thus far, however, it does not seem likely that excessive secretion of estrogens frequently plays any major role in the expressions of adrenal tumors in man.

#### THE URINARY EXCRETORY PRODUCTS

Pineus and Hirschmann<sup>103</sup> have recently provided a complete review of the urinary derivatives of the biologically active steroid compounds, and Koch<sup>104</sup> and Doisy<sup>105</sup> have discussed the intermediary metabolism of the androgens and estrogens, respectively. When studies of urinary hormonal or better hormonelike substances were initiated, it was hoped that the pathologic physiology of much human disease would be promptly clarified. The upshot has been otherwise. A new and complex body of data appeared, related it is true to the expressions of disease, but related through the still obscure processes of the intermediary metabolism of the steroids. It is accordingly not possible now to read the hormone circulating in the body directly from a urinary assay, however painstaking such assay may be from the technical standpoint. Urinary studies form such a large part of the means by which the pathologic physiology of adrenal tumors will be eventually unraveled, however, that consideration will be given here to the available data. Unfortunately, the thoroughgoing and elaborate undertaking of Dobriner, Gordon, Lieberman, Fieser, and Rhoads which promises so much for the crystallization of our knowledge of this subject has been published only in preliminary form.<sup>106</sup>

The chief normal urinary steroids of 19-carbon atom series are:

1. androsterone (XIV)
2. etiocholan 3 $\alpha$  ol 17 one (XVI)

## 3. dehydroisoandrosterone (XV)

## 4. isoandrosterone

Of these, androsterone and its stereoisomer etiocholan-ol-one are present in approximately equal amounts. Dobriner has kindly permitted me to quote the unpublished figures of his group as obtained by isolation procedures. Three normal young men excreted from 5.2 to 6.6 mg. of androsterone per day and from 4.9 to 8.1 mg. of etiocholan-ol-one per day. Two normal young women excreted from 3.0 to 3.1 mg. of androsterone and from 2.9 to 3.1 mg. of etiocholan-ol-one per day. Of these, androsterone alone is androgenic and accounts thus for the bulk of the androgenic activity of normal urine, which by the capon comb technique amounts to about 70 International Units per day (7 mg. equivalents of androsterone) in normal young men and somewhat less, in all probability, in normal young women. Dehydroisoandrosterone and isoandrosterone possess the  $\beta$  configuration at carbon 3 and are hence digitonin precipitable. Talbot and his associates<sup>107</sup> and Bauman and Metzger<sup>108</sup> give this  $\beta$  fraction as 10 per cent or less of the total 17-ketosteroids on the average. Dobriner's estimates are lower, while Munson, Gallagher, and Koch<sup>109</sup> account for about 20 per cent of the total 17-ketosteroids as dehydroisoandrosterone sulfate. Since dehydroisoandrosterone is from one-half to one-third as potent as androsterone and isoandrosterone about one-fifth as potent by the capon comb technique, these substances do not contribute greatly to the androgenicity of normal urine.

All of these steroids are present as conjugates which are biologically inactive, dehydroisoandrosterone as the sulfate,<sup>109</sup> and others possibly as glucuronides. They are freed by hydrolysis. Taken together they are commonly known as 17-ketosteroids, and measured as such, doubtless with other substances, by the red color given with metadinitrobenzene (Zimmerman reaction). They fall into the ketonic and alcoholic fractions, which make up the greater part of the mixture in normal urine yielding this color.

As determined first by the Callows,<sup>110, 111</sup> the components of the steroid mixture in the urine of normal men and women are the same, such difference as exists being quantitative, rather than qualitative. When testosterone is administered, the urinary excretion of at least androsterone and etiocholan-ol-one is increased<sup>112, 113</sup> so that these substances may be derived in part at least from the testis. Similarly, in the urine of a patient with a malignant interstitial cell tumor of the testis studied by Venning, Hoffman, and Browne<sup>114</sup> large amounts of androsterone sulfate were found. Neither in this patient nor in those receiving injections of testosterone was dehydroisoandrosterone part of the increment in urinary steroids. Castrated men<sup>115</sup> and women<sup>116</sup> excrete much the same type of 17-ketosteroids as normal men and

women. Castrated or sexually underdeveloped men have less androgenic activity in the urine than normal young men<sup>117-119</sup> but the overlap is substantial. The situation in castrated women is less clear. Total 17-ketosteroid excretion seems unaffected<sup>120, 121</sup> but androgens have been insufficiently studied. Quantitative variations in the amounts of the several steroids before and after castration in either sex, require much further study as exemplified by the anomalous rise in 17-ketosteroid excretion occurring late after the castration of older men in the experience of Scott and Vermeulen.<sup>141</sup> In Addison's disease 17-ketosteroid and androgen excretion is low probably especially in women.<sup>120</sup> The matter may be summarized by the statement that while part of the urinary androsterone and etiocholan-ol-one arises from the testis in the male that a nongonadal source must be sought for the remainder, and that a nongonadal source likewise must be sought for much if not all of similar compounds in the female. No gonadal source for dehydroisoandrosterone has been established. The adrenal by virtue of the steroid character of its hormones comes naturally to mind as a source for these substances.

The urine of patients with adrenal cancer has long been known to contain often excessive amounts of androgenic material.<sup>117</sup> Callow<sup>122, 123</sup> first examined the nature of the androgens present. In a 6-year-old girl exhibiting a Cushing type of disorder as much as 70 mg. of dehydroisoandrosterone was obtained from a liter of urine, as compared to 0.1 to 0.2 mg. per liter obtained from normal adults. The dehydroisoandrosterone accounted for 70 per cent of the androgenic activity. Callow observed this in other patients and it has been confirmed further by Wolfe, Fieser, and Friedgood<sup>124</sup> and Dorfman and associates<sup>125</sup> by isolation procedures and approximately by Talbot<sup>107, 127</sup> and Dobriner<sup>106</sup> and their respective associates measuring the 3- $\beta$  or digitonin precipitable fractions of urine. It is not known whether dehydroisoandrosterone is secreted as such or whether it is derived from some precursor. No injected steroid save dehydroisoandrosterone itself<sup>109</sup> has been shown to yield this steroid in the urine although examination of the matter must be said to be fragmentary thus far. Nor is it clear that excessive excretion of 3- $\beta$  steroids can be correlated with any particular clinical expression of the disease. In Cushing's syndrome not due to adrenal tumors, 17-ketosteroid excretion may be normal<sup>120</sup> and the  $\beta$  fraction not unusual.<sup>107</sup> In adrenal tumors producing the more strictly adrogenital form of disorder, dehydroisoandrosterone excretion<sup>125</sup> or  $\beta$  fraction excretion has been high. It has by no means been shown that all increased androgenic activity in the urine of subjects with adrenal tumors or hyperplasia is consistently due to dehydroisoandrosterone. Androsterone may contribute to the enhanced activity. The physiologic potentialities of dehydroisoandrosterone itself in man are insufficiently explored so that it is not possible to envisage clearly the effects of this material in patients with adrenal tumors.



Others of the 17-ketosteroids may be present in excess in patients with adrenal tumors. Etiocholan-ol-one was greatly increased in the urine of a subject reported by Wolfe, Fieser, and Friedgood<sup>124</sup> at a time when little androsterone was present. The significance of this is uncertain.  $\delta$ -3-5 androstadienone-17 has been found on several occasions both in feminizing<sup>125</sup> and masculinizing tumors<sup>122</sup> and the presence of this and other poorly understood substances either excreted directly or arising in the course of manipulation of the urine requires explanation. Talbot, Butler, and Berman<sup>127</sup> report unusual amounts of nonalcoholic 17-ketosteroids in patients with cancer of the adrenal as compared with those with adrenal hyperplasia.

It may be held as likely that none of the adrenal hormones serving to maintain life contribute materially to the urinary 17-ketosteroids. This presumption is possible even in the absence of suitable experiments in which adrenal steroids have been injected into man and their derivatives followed in the urine. Children excrete very little 17-ketosteroid or androgenic material in their urine. The increase in these substances in both sexes at puberty bespeaks some function evolving at that time and not some function essential to life. As mentioned previously, the adrenal function involved may have something to do with secondary sex characters or with anabolic effects like those of testosterone. This matter may be considered uncertain at present. It must be noted that urinary androgens are excreted as biologically active conjugates and those events that are of utmost physiologic importance occur prior to this conjugation.

Anderson and her associates<sup>48</sup> first presented evidence that a life-sustaining, adrenocortical-like compound was present in excessive amounts in the blood and urine of patients with Cushing's syndrome. Weil and Browne<sup>128</sup> using Selye and Schenker's<sup>129</sup> test of improvement in the endurance to cold of adrenalectomized rats found cortical material in the urine of several patients including those subjected to operations. This test has been further utilized by Dorfman and his colleagues<sup>130</sup> and by the Montreal group,<sup>131</sup> and a substance or substances found in normal urine which will sustain life of adrenalectomized rats, improve tolerance to cold, increase resistance to fatigue in electrically stimulated muscle, and increase liver glycogen. These are the properties of adrenal extracts and taken together suggest the presence of a corticosterone-like compound. The further application of such biologic tests to the urine of patients with adrenal tumors will be of importance.

Biologically inactive alcohols of the 21-carbon atom series have been isolated from the urine of patients with adrenal tumors or adrenal hyperplasia. Butler and Marrian<sup>132</sup> isolated pregnane-3, 17, 20-triol from the urine of women with virilism. Venning, Weil, and Browne<sup>133</sup> later found substantial amounts of pregnanediol glucuronide in the

urine of a woman with an adrenal tumor in which there was no vestige of ovarian function. This has now been repeatedly confirmed both in girls and women with adrenal hyperplasia,<sup>67, 127</sup> although it is not a constant finding.<sup>127</sup> Since progesterone is the source of this substance in the latter half of the normal menstrual cycle and since progesterone has been found in the adrenal cortex, this substance could be the precursor in patients with adrenal hyperfunction. Desoxycorticosterone likewise yields urinary pregnanediol glucuronide however<sup>134</sup> and other steroids may do so. Thus far the appearance of pregnanediol does not seem to be strictly correlated with any special type of clinical disorder, appearing both in intensely masculinized girls showing little or none of the Cushing phenomena<sup>127</sup> and in woman with the typical Cushing syndrome.<sup>67</sup>

Frank<sup>135</sup> demonstrated the presence of large amounts of estrogens in the urine of a masculinized woman with an adrenal cortical carcinoma. This seems to be an infrequent finding.<sup>117</sup> Simpson and Joll<sup>136</sup> demonstrated large amounts of estrogenic activity in the urine of a man with a feminizing tumor establishing a correlation with the symptoms and signs of the disorder. Frank's experience is frankly paradoxical. One must conclude that in his case conjugation of the estrogens occurred before an opportunity to influence the organism was provided. Estrone is present in the adrenal cortex but other steroids may yield estrogens somewhere in the course of their activity. Testosterone propionate, for example, has repeatedly been shown to do so.

The confusion surrounding the physiologic meaning of the urinary excretion of steroids will be gradually surmounted as more of the adrenal agents become available in sufficient amount and in sufficient purity for administration to man. The economy of lower species with respect to urinary steroids is so different from that of the human being that little directly applicable information is to be gained from them.

#### MISCELLANEOUS

It is a common and dangerous experience to find the contralateral adrenal gland atrophic in the presence of an adrenal cortical tumor. Cahill and his associates<sup>34</sup> and Thompson and Eisenhardt<sup>35</sup> have pointed out that this atrophy is likely to be profound when the clinical expressions of the disease are those of Cushing's syndrome and is less conspicuous in the adrenogenital syndrome. Experimental findings are in accord with this distinction. Cortical extracts induce atrophy of the normal adrenals, an influence which may be exerted through inhibition of pituitary adrenotropic secretion, since pituitary adrenotropins will prevent this adrenal inhibition. Corticosterone and 11-dehydro-17-hydroxycorticosterone seem most effective in this regard, desoxycorticosterone less so, although the latter compound in Selye's

experience will induce atrophy in large dosage. The androgens do not materially inhibit the adrenal cortex, save in the case of specialized X zone of the mouse. It is therefore reasonable that victims of tumors in which masculinization predominates should have better preserved cortical tissue than those in which excess of the more typical adrenal secretions exists.

Several cortical steroids and cortical extracts as well as the gonadal hormones induce atrophy of the thymus gland in experimental animals. Thymic involution, however, is so common in man with all types of illness that it will be impossible to relate thymic involution to the expressions of adrenal tumors with any degree of accuracy. Occasional exceptions to this expected thymic involution are, however, of a good deal of theoretical interest. Thus, Freyberg's patient<sup>85</sup> with manifest Cushing's syndrome and atrophic adrenals had a very large thymus. The chief lesion in this instance was a pituitary adenoma. One cannot help but raise the question as to whether the manifestations of the disorder were not due to direct pituitary influence on tissues rather than to increased adrenal secretion secondary to pituitary stimulation. Thymic involution would have been expected had the syndrome been due to excess of compounds like corticosterone.

This same question has been raised by Crooke,<sup>137</sup> who described hyalinization of pituitary basophiles in Cushing's syndrome irrespective of whether adrenal tumors, adrenal hyperplasia, pituitary tumors, or thymic tumors were present or not. Students of the subject have generally come to agree with Crooke's findings, and Thompson and Eisenhardt have stressed the uniformity of these basophile changes in patients with adrenal tumors in which Cushing's syndrome was fully evolved. The disposition, however, to see in this common lesion an expression of pituitary hyperactivity and to attribute many of the expressions of the disease to pituitary hyperfunction has not found favor. The reasons for this are obvious enough. Cytologists have not been able to agree as to whether the Crooke changes represent increased secretory function or whether they are degenerative. Adrenotropic pituitary secretions are well known and the functions of the adrenal under such stimulation seem much like those of large amounts of cortical extract, or of adrenal steroids in excess. Very little is known of the reverse influence of the adrenal cortex on the pituitary body. Most effects of adrenal extracts on carbohydrate metabolism seem well exhibited in the hypophysectomized animal.<sup>8</sup> With the exception of the capacity to induce atrophy of the normal adrenal cortex, few if any of the properties of adrenal steroids are known to be exerted through the anterior lobe. When a chain of events occurs, therefore, in which both pituitary and adrenal cortex are involved, one is at the present time most likely to consider the pituitary as stimulating the adrenal cortex rather than the reverse. It must be admitted, however, that patients

like that of Freyberg and his associates<sup>55</sup> are somewhat disquieting. Further attention to the Crooke phenomena will doubtless be given in the future and attempts to induce the hyalin changes in pituitary basophiles with pure adrenal steroids in excess will be made. If such can be done and the effects correlated with physiologic response in normal and hypophysectomized animals the extent to which the particular steroid operates through the hypophysis can be determined. Until such work is accomplished it will be difficult to rest easy in our usual assumption that most of the expressions of adrenal tumors are due to the direct peripheral action of the adrenal steroids. The occasional presence of advanced spermatogenesis in boys with precocious puberty due to adrenal tumors speaks to the same point, since the question of participation of the hypophysis must be raised and for the present left unanswered.

#### SUMMARY

1. Some twenty-eight compounds have now been isolated from the suprarenal cortex. A number of these such as corticosterone and desoxycorticosterone effectively repair those disturbances of salt and water metabolism characteristic of suprarenal insufficiency. Those with an oxygen at carbon 11, such as corticosterone and 17-hydroxy-11-dehydrocorticosterone, repair defects in carbohydrate and protein metabolism characteristic of suprarenal insufficiency. Certain of the 17-hydroxyl compounds favor urinary sodium and chloride loss. An amorphous fraction has been isolated which is more powerful in sustaining the life of the adrenalectomized dog than any known pure steroid. Progesterone, several androgens, estrone, and several compounds, inert by biological assays thus far made, have also been obtained.

2. It is likely that at least two secretions are necessary to repair suprarenal defects and that androgenic or estrogenic functions require the formation of separate differentiated hormones.

3. The following signs and symptoms of adrenal tumors have been reproduced to some extent by pure steroids:

- (a) Hypertension by desoxycorticosterone acetate.
- (b) Sodium, chloride, and water retention and potassium loss by desoxycorticosterone and corticosterone. The electrolyte pattern in the serum of patients, however, is not completely accounted for by these steroids.
- (c) Diabetes mellitus and nitrogen loss by compounds such as corticosterone and 17-hydroxy-11-dehydrocorticosterone, especially in the presence of reduced insulin secretion.
- (d) Nitrogen retention and somatic growth by testosterone and its relatives.
- (e) The masculinization and the feminization, respectively, together with depression of gonadal function, by androgens and estrogens.

- (f) Atrophy of the contralateral adrenal cortex by corticosterone and 17-hydroxy-11-dehydrocorticosterone.

It is pointed out that metabolic balances in the victims of adrenal tumors are often meager and that such balances may be expected to vary from person to person depending on the active steroids secreted. The known steroids may serve to counterbalance one another if mixed in proper proportion by the tumor.

4. The following signs and symptoms of adrenal tumors are not yet accounted for although hypotheses exist which promise with suitable modification, to be useful in the future.

- (a) The osteoporosis
- (b) Cutaneous rubor, striae, and ecchymoses
- (c) Adiposity
- (d) Polyuria and polydipsia
- (e) Muscular weakness

5. A number of interesting steroids have been found in excessive amounts in the urine of the victims of adrenal tumors. The precursors of these steroids and their function in the body are, however, obscure.

6. Further elaboration of almost every point is necessary before the actual secretions of adrenal tumors can be identified. The suggestions made in the foregoing are often the merest approximations and indicate the direction that contemporary research is taking toward the solution of the problems involved.

#### REFERENCES

1. Kendall, E. C.: *Function of the Adrenal Cortex, Glandular Physiology and Therapy*, Chap. 18, Chicago, 1942, American Medical Association, p. 273.
2. Reichstein, T., and Shoppee, C. W.: *The Hormones of the Adrenal Cortex, Vitamins & Hormones* 1: 345, 1943.
3. Pfaffner, J. J.: *The Adrenal Cortical Hormones*, *Advances Enzymol.* 2: 325, 1942.
4. Kendall, E. C.: *Hormones of the Adrenal Cortex*, *Endocrinology* 30: 853, 1942.
5. Kendall, E. C.: *Hormones*, *Ann. Rev. Biochem.* 10: 285, 1941.
6. Kendall, E. C.: *The Adrenal Cortex*, *Arch. Path.* 32: 474, 1941.
7. Long, C. N. H.: *A Discussion of the Mechanism of Action of Adrenal Cortical Hormones on Carbohydrate and Protein Metabolism*, *Endocrinology* 30: 870, 1942.
8. Long, C. N. H., Katzin, B., and Fry, E. G.: *Adrenal Cortex and Carbohydrate Metabolism*, *Endocrinology* 26: 309, 1940.
9. Ingle, D. J.: *Problems Relating to the Adrenal Cortex*, *Endocrinology* 31: 419, 1942.
10. Thorn, G. W., Engel, L. L., and Eisenberg, H.: *The Effect of Corticosterone and Related Compounds on the Renal Excretion of Electrolytes*, *J. Exper. Med.* 68: 161, 1938.
11. Ferrebee, J. W., Ragan, Charles, Atchley, D. W., and Loeb, R. F.: *Desoxycorticosterone Esters: Certain Effects in the Treatment of Addison's Disease*, *J. A. M. A.* 113: 1725, 1939.
12. Thorn, G. W., Dorrance, S. S., and Day, E.: *Addison's Disease: Evaluation of Synthetic Desoxycorticosterone Acetate Therapy in 158 Patients*, *Ann. Int. Med.* 16: 1053, 1942.

13. Ferrebee, J. W., Ragan, C., Atchley, D. W., and Loeb, R. F.: A Comparison of Certain Effects of Desoxycorticosterone Acetate, Corticosterone and Cortical Extract on a Patient With Addison's Disease, *Endocrinology* 27: 360, 1940.
14. Swingle, W. W., Remington, J. W., Drill, V. A., and Kleinberg, W.: Differences Among Adrenal Steroids in Protecting the Adrenalectomized Dog Against Circulatory Failure, *Am. J. Physiol.* 136: 567, 1942.
15. Thorn, G. W., Koepf, G. F., Lewis, R. A., and Olsen, E. F.: Carbohydrate Metabolism in Addison's Disease, *J. Clin. Investigation* 19: 813, 1940.
16. Thorn, G. W., and Clinton, M., Jr.: Metabolic Changes in a Patient With Addison's Disease Following the Onset of Diabetes Mellitus, *J. Clin. Endocrinol.* 3: 335, 1943.
17. Ingle, D. J., and Thorn, G. W.: A Comparison of the Effects of 11-Desoxycorticosterone Acetate and 17-Hydroxy-11-Dehydrocorticosterone in Partially Pancreatized Rats, *Am. J. Physiol.* 132: 670, 1941.
18. Thorn, G. W., Engel, L. L., and Lewis, R. A.: The Effect of 17-Hydroxycorticosterone and Related Adrenal Cortical Steroids on Sodium and Chloride Excretion, *Science* 10: 348, 1941.
19. Lewis, R. A., Thorn, G. W., Koepf, G. F., and Dorrance, S. S.: The Role of the Adrenal Cortex in Acute Anoxia, *J. Clin. Investigation* 21: 33, 1942.
20. Selye, H.: Compensatory Atrophy of the Adrenals, *J. A. M. A.* 115: 2246, 1940.
21. Wells, B. B., and Kendall, E. C.: Qualitative Difference in the Effect of Compounds Separated From the Adrenal Cortex on Distribution of Electrolytes and on Atrophy of the Adrenal and Thymus Glands of Rats, *Proc. Staff Meet., Mayo Clin.* 15: 133, 1940.
22. Wells, B. B., and Kendall, E. C.: The Influence of Corticosterone and C-17-Dehydrocorticosterone (Compound E) on Somatic Growth, *Proc. Staff Meet., Mayo Clin.* 15: 324, 1940.
23. Carnes, W. H., Ragan, C., Ferrebee, J. W., and O'Neill, J.: Effects of Desoxycorticosterone Acetate in the Albino Rat, *Endocrinology* 29: 144, 1941.
24. Houssay, B. A.: Advancement of Knowledge of the Role of the Hypophysis in Carbohydrate Metabolism During the Last Twenty-five Years, *Endocrinology* 30: 884, 1942.
25. Albright, Fuller, Parson, W., and Bloomberg, E.: Cushing's Syndrome Interpreted as Hyperadrenocorticism Leading to Hypergluconeogenesis, *J. Clin. Endocrinol.* 1: 375, 1941.
26. Kuizenga, M. H., and Cartland, G. F.: Fractionation Studies on Adrenal Cortex Extract With Notes on the Distribution of Biological Activity Among the Crystalline and Amorphous Fractions, *Endocrinology* 24: 526, 1939.
27. Li, C. H., Simpson, M. E., and Evans, H. M.: Isolation of Adrenocorticotrophic Hormone From Sheep Pituitaries, *Science* 96: 450, 1942.
28. Li, C. H., Evans, H. M., and Simpson, M. E.: Adrenocorticotrophic Hormone, *J. Biol. Chem.* 149: 413, 1943.
29. Sayers, G., White, A., and Long, C. N. H.: Preparation and Properties of Pituitary Adrenotropic Hormone, *J. Biol. Chem.* 149: 425, 1943.
30. Dougherty, T. P., and White, A.: Effect of Adrenotropic Hormone on Lymphoid Tissue, *Proc. Soc. Exper. Biol. & Med.* 53: 132, 1943.
31. Marx, W., Simpson, M. E., Li, C. H., and Evans, H. M.: Antagonism of Pituitary Adrenocorticotrophic Hormone to Growth Hormone in Hypophysectomized Rats, *Endocrinology* 33: 102, 1943.
32. Kepler, E. J., and Keating, F. R.: Diseases of the Adrenal Glands. II. Tumors of the Adrenal Cortex, Diseases of the Adrenal Medulla and Allied Disturbances, *Arch. Int. Med.* 68: 1010, 1941.
33. Haymaker, Webb, and Anderson, E.: The Adrenogenital and Cushing's Syndrome, *Internat. Clin. (N.S.)* 4: 244, 1938.
34. Cahill, G. F., Mellicow, M. M., and Darby, H. H.: Adrenal Cortical Tumors; Types of Non-hormonal and Hormonal Tumors, *Surg., Gynec. & Obst.* 74: 281, 1942.
35. Thompson, K. W., and Eisenhardt, T.: Further Consideration of Cushing's Syndrome, *J. Clin. Endocrinol.* 3: 445, 1943.
36. Marks, T. M., Thomas, J. M., and Warkany, J.: Adrenocortical Obesity in Children, *Am. J. Dis. Child.* 60: 923, 1940.
37. Thompson, W. O., Thompson, P. K., Taylor, S. G. III, and Hoffman, W. S.: Treatment of Addison's Disease With Desoxycorticosterone Acetate, *Proc. Central Soc. Clinical Research*, 1939.

38. McCullagh, E. P., and Ryan, E. J.: The Use of Desoxycorticosterone Acetate in Addison's Disease, *J. A. M. A.* 114: 2530, 1940.
39. Thorn, G. W., and Firor, W. M.: Desoxycorticosterone Acetate Therapy in Addison's Disease. Clinical Consideration, *J. A. M. A.* 114: 2517, 1940.
40. Loeb, R. F.: The Adrenal Cortex and Electrolyte Behavior, *Harvey Lectures* 37: 100, 1941-42.
41. Swingle, W. W., Parkins, W. M., and Remington, J. W.: Effects of Desoxycorticosterone Acetate and Blood Serum Transfusions Upon Circulation of Adrenalectomized Dog, *Am. J. Physiol.* 134: 503, 1941.
42. Kuhlman, D., Ragan, C., Ferrebee, S. W., Atchley, D. W., and Loeb, R. F.: Toxic Effects of Desoxycorticosterone Esters in Dogs, *Science* 110: 496, 1939.
43. Grollman, A., Harrison, T. R., and Williams, J. R.: Effects of Various Sterol Derivatives on Blood Pressure of Rat, *J. Pharmacol. and Exper. Therap.* 69: 149, 1940.
44. Kepler, E. J.: Symposium Polyglandular Dyscrasias Involving Abnormalities of Sexual Characteristics; Report of Four Cases (Case 4), *Proc. Staff Meet., Mayo Clin.* 8: 102, 1933.
45. Walters, W., Wilder, R. M., and Kepler, E. J.: The Suprarenal Cortical Syndrome; Report of Two Cases With Successful Surgical Treatment, *Proc. Staff Meet., Mayo Clin.* 9: 400, 661, 1934.
46. McQuarrie, J., Johnson, M. H., and Ziegler, M. R.: Plasma Electrolyte Disturbance in a Patient With Hypercortico Adrenal Syndrome Contrasted With That Found in Addison's Disease, *Endocrinology* 21: 762, 1937.
47. Willson, D. M., Power, M. H., and Kepler, E. J.: Alkalosis and Low Plasma Potassium in a Case of Cushing's Syndrome, *J. Clin. Investigation* 40: 701, 1940.
48. Anderson, E., Haymaker, W., and Joseph, M.: Hormone and Electrolyte Studies of Patients With Hyperadrenocortical Syndrome (Cushing's Syndrome), *Endocrinology* 23: 398, 1938.
49. Howard, J. E., and Whitehead, M. R.: Virilism, *Internat. Clin. (N.S.)* 4: 51, 1938.
50. Ragan, C., Ferrebee, J. W., Atchley, D. W., and Loeb, R. F.: A Syndrome of Polydipsia and Polyuria Induced in Normal Animals by Desoxycorticosterone, *Am. J. Physiol.* 131: 73, 1940-41.
51. Ferrebee, J. W., Parker, D., Carnes, W. H., Gerity, M. K., Atchley, D. W., and Loeb, R. F.: Certain Effect of Desoxycorticosterone. The Development of "Diabetes Insipidus" and the Replacement of Muscle Potassium by Sodium in Normal Dogs, *Am. J. Physiol.* 135: 230, 1941-42.
52. Miller, H. C., and Darrow, D. C.: Relation of Muscle Electrolyte to Alterations in Serum Potassium and to Toxic Effects of Injected Potassium Chloride, *Am. J. Physiol.* 130: 747, 1940.
53. Winter, C. A., and Ingram, W. R.: Observations on the Polyuria Produced by Desoxycorticosterone Acetate, *Am. J. Physiol.* 139: 710, 1943.
54. Darrow, D. C., and Miller, H. C.: The Production of Cardiac Lesions by Repeated Injections of Desoxycorticosterone Acetate, *J. Clin. Investigation* 21: 601, 1942.
55. Moehlig, R. C., and Jaffe, Louis: Syndrome Simulating Diabetes Insipidus in Dogs Induced by Desoxycorticosterone Acetate; Clinical Observation of Syndrome With Addition of Tetany, *J. Lab. & Clin. Med.* 27: 1009, 1942.
56. Heppel, T. A.: The Electrolytes in Muscle and Liver of Potassium Depleted Rats, *Am. J. Physiol.* 127: 385, 1939.
57. Thorn, G. W., and Engel, L. L.: The Effect of Sex Hormones on the Renal Excretion of Electrolytes, *J. Exper. Med.* 68: 299, 1938.
58. Kenyon, A. T., Sandiford, I., Bryan, A. H., Knowlton, K., and Koch, F. C.: The Effect of Testosterone Propionate on Nitrogen, Electrolyte, Water and Energy Metabolism in Eunuchoidism, *Endocrinology* 23: 135, 1938.
59. Talbot, N. B., and Butler, A. M., and MacLachlan, E. A.: The Effect of Testosterone and Allied Compounds on the Mineral, Nitrogen and Carbohydrate Metabolism of a Girl With Addison's Disease, *J. Clin. Investigation* 21: 583, 1943.
60. Newburgh, L. H.: Obesity, *Arch. Int. Med.* 70: 1033, 1942.
61. Freyberg, R. H., and Newburgh, L. H.: The Obesity and Energy Exchange in a Verified Case of Pituitary Basophilism, *Arch. Int. Med.* 58: 229, 1936.
62. Fry, E. G.: The Effect of Adrenalectomy and Thyroidectomy on Ketouria and Liver Fat Content of the Albino Rat Following Injections of Anterior Pituitary Extract, *Endocrinology* 21: 283, 1937.

- Fry, E. G., MacKay, E. M., and Barnes, R. H.: Effect of Adrenalectomy on Liver Fat in Fasting and After Administration of Anterior Pituitary Extracts, *Am. J. Physiol.* 118: 525, 1937.
63. Lukens, F. D. W., Flippin, H. F., and Thigpen, F. M.: Adrenal Cortical Adenoma With Absence of the Opposite Adrenal, *Am. J. M. Sc.* 193: 812, 1937.
64. Sheppardson, H. C., and Shapiro, Edward: The Diabetes of Bearded Women, *Endocrinology* 24: 237, 1939.
65. Sprague, R. G., Priestley, J. T., and Dockerty, M. B.: Diabetes Mellitus Without Other Endocrine Manifestations in a Case of Tumor of the Adrenal Cortex, *J. Clin. Endocrinol.* 3: 128, 1943.
66. Fraser, R., Albright, F., and Smith, P. H.: The Value of the Glucose Tolerance Test, Insulin Tolerance Test and the Glucose Insulin Tolerance Test in the Diagnosis of Endocrinologic Disorders of Glucose Metabolism, *J. Clin. Endocrinol.* 1: 297, 1941.
67. Paschkis, K. E., Herbert, P. A., Rakoff, A. E., and Cantorow, A.: A Case of Cushing's Syndrome With Adrenal Hyperplasia, Without Pituitary Basophilic Adenoma or Hyperplasia, *J. Clin. Endocrinol.* 3: 212, 1943.
68. Woodvatt, R. T., quoted by Cushing, H.: The Basophile Adenomas of the Pituitary Body and Their Clinical Manifestations ("Pituitary Basophilism") in "Pituitary Body and Hypothalamus," *Bull. Johns Hopkins Hosp.* 50: 137-195, 1932.
69. Ingle, D. J.: The Production of Glycosuria in the Normal Rat by Means of 17-Hydroxy-11 Dehydrocorticosterone, *Endocrinology* 29: 649, 1941.
70. Kenyon, A. T., Knowlton, K., Sandiford, I., Koch, F. C., and Lotwin, G.: A Comparative Study of the Metabolic Effects of Testosterone Propionate in Normal Men and Women in Eunuchoidism, *Endocrinology* 26: 26, 1940.
71. Albright, Fuller: Cushing's Syndrome, *Harvey Lectures* 38: 1942-43. (In press.)
72. Jones, R., McCullagh, E. P., McCullagh, D. R., and Buckaloo, G. W.: Methyl Testosterone IV. Observations on the Hypermetabolism Induced by Methyl Testosterone, *J. Clin. Endocrinol.* 1: 656, 1941.
73. Wilkins, L., Fleischmann, W., and Howard, J. E.: Creatinuria Induced by Methyl Testosterone in Dwarfed Boys and Girls, *Bull. Johns Hopkins Hosp.* 69: 493, 1941.
74. Kenyon, A. T., Knowlton, K., Lotwin, G., Munson, P. T., Johnston, C. D., and Koch, F. C.: Comparison of Metabolic Effects of Testosterone Propionate With Those of Chorionic Gonadotropin, *J. Clin. Endocrinol.* 2: 685, 1942.
75. Knowlton, K., Kenyon, A. T., Sandiford, J., Lotwin, G., and Fricker, L.: Comparative Study of Metabolic Effects of Estradiol Benzoate and Testosterone Propionate in Man, *J. Clin. Endocrinol.* 2: 771, 1942.
76. Webster, B., and Hoskins, W. N.: Influence of Androgen Therapy on Growth Rate of Hypogonadal Adolescent Boys, *Proc. Soc. Exper. Biol. & Med.* 45: 72, 1940.
77. Browne, J. S. L., and Ross, A.: Influence of Testosterone Propionate on Cases of Retarded Growth, *Proc. Assoc. Study Intern. Secretions*, 1941.
78. Thompson, W. O., Heckel, N. J., and Morris, R. M.: Hormonal Factors Influencing Skeletal Growth, *Tr. A. Am. Physicians* 57: 216, 1942.
79. McCullagh, E. P., and Rossmiller, H. R.: Methyl Testosterone; Effect on Body Weight and Growth, *J. Clin. Endocrinol.* 1: 507, 1941.
80. Dorff, G. B.: Rapid Growth in Height Produced by Chorionic Gonadotropin in Dwarfed Identical Twin, *J. Clin. Endocrinol.* 1: 940, 1941.
81. Albright, F., Bloomberg, E., and Smith, P. H.: Post-menopausal Osteoporosis, *Tr. A. Am. Physicians* 15: 298, 1940.
82. Kenyon, A. T.: The Comparative Metabolic Influences of the Testicular and Ovarian Hormones, *Biol. Symposia* 9: 11, 1942.
83. Wilkins, L., Fleischmann, W., and Howard, J. E.: Macrogonitosomia Precox Associated With Hyperplasia of the Androgenic Tissue of the Adrenal and Death From Cortico-Adrenal Insufficiency, *Endocrinology* 26: 385, 1940.
84. Butler, A. M., Ross, R. A., and Talbot, N. B.: Probable Adrenal Insufficiency in an Infant, *J. Pediat.* 15: 831, 1939.
85. Freyberg, R. H., Barker, P. S., Newburgh, L. H., and Collier, F. A.: Pituitary Basophilism (Cushing's Syndrome): Report of a Verified Case With a Discussion of the Differential Diagnosis and Treatment, *Arch. Int. Med.* 58: 187, 1936.



86. Freyberg, R. H., and Grant, R. L.: Calcium and Phosphorus Metabolism in a Verified Case of Pituitary Basophilism, *Arch. Int. Med.* 58: 213, 1936.
87. Aub, J. C., and Tibbetts, D. M.: Do Pituitary and Adrenal Glands Influence Calcium or Magnesium Metabolism? *Tr. A. Am. Physicians* 51: 129, 1936.
88. Reifenstein, E. C., Jr., Albright, F., Parson, W., and Bloomberg, E.: The Effect of Estradiol Benzoate and of Testosterone Propionate and of Combinations of Both on Post Menopausal Osteoporosis and Senile Osteoporosis, *Endocrinology* 30: 1024, 1942.
89. Geist, S. H., Salmon, U. J., Gaines, J. A., and Walter, R. I.: The Biologic Effects of Androgen (Testosterone Propionate) in Women, *J. A. M. A.* 114: 1539, 1940.
90. Papanicolaou, G. N., Ripley, H. S., and Shorr, E.: Suppressive Action of Testosterone Propionate on Menstruation and Its Effect on Vaginal Smears, *Endocrinology* 24: 339, 1939.
91. Shorr, E., Papanicolaou, G., and Stimenel, B.: Neutralization of Ovarian Follicular Hormone in Women in Simultaneous Administration of Male Sex Hormone, *Proc. Soc. Exper. Biol. & Med.* 38: 759, 1938.
92. Heckel, N. J.: Influence of Testosterone Propionate Upon Benign Prostatic Hypertrophy and Spermatogenesis; a Clinical and Pathological Study in the Human, *J. Urol.* 43: 286, 1940.
93. Price, D.: Normal Development of the Prostate and Seminal Vesicles of the Rat With a Study of Experimental Post-natal Modifications, *Am. J. Anat.* 60: 79, 1936.
94. Davidson, C. S., and Moon, H. D.: Effect of Adrenocorticotrophic Extracts in Accessory Reproductive Organs of Castrate Rats, *Proc. Soc. Exper. Biol. & Med.* 35: 281, 1936.
95. Howard-Miller, E.: A Transitory Zone in the Adrenal Cortex Which Shows Age and Sex Relationships, *Am. J. Anat.* 40: 251, 1927.
96. Deanesley, R., and Parkes, A. S.: Multiple Activities of Androgenic Compounds, *Quart. J. Exper. Physiol.* 26: 393, 1937.
97. Grollman, A.: The Adrenals, Baltimore, 1936, Williams & Wilkins Company.
98. Burrill, M. W., and Greene, R. R.: Androgenic Function of the Adrenals in the Immature Male Castrate Rat, *Proc. Soc. Exper. Biol. & Med.* 40: 327, 1939.
99. Broster, L. R., Allen, C., Vines, H. W. C., Patterson, J., Greenwood, A. W., Marrian, G. F., and Butler, G. C.: The Adrenal Cortex and Intersexuality, London, 1938, Chapman & Hall, Ltd., pp. 257.
100. Goormatigh, N.: Cytology of Functioning Adrenal Tumors, *Am. J. Cancer* 38: 32, 1940.
101. Gardner, W. U.: Estrogenic Effects of Adrenal Tumors of Ovariectomized Mice, *Cancer Research* 1: 632, 1941.
102. Shorr, E., Bernheim, A. R., and Tausky, H.: The Relation of Urinary Citric Acid to the Menstrual Cycle and the Steroidal Reproductive Hormones, *Science* 95: 606, 1942.
103. Pincus, G., and Hirschmann, W. H.: The Intermediate Metabolism of the Sex Hormones, *Vitamins & Hormones* 1: 293, 1943.
104. Koch, F. C.: The Excretion and Metabolism of Male Sex Hormones in Health and Disease, *Biol. Symposia* 9: 41, 1942.
105. Doisy, E. A.: The Metabolism of Estrogens, *Biol. Symposia* 9: 21, 1942.
106. Dobriner, K., Gordon, E., Rhoads, C. P., Lieberman, S., and Fieser, S. F.: Steroid Hormone Excretion by Normal and Pathological Individuals, *Science* 95: 534, 1942.
107. Talbot, N. B., Butler, A. M., and MacLachlan, E. A.: Alpha and Beta Neutral Ketosteroids (Androgens). Preliminary Observations on Their Normal Urinary Excretion and on the Clinical Usefulness of Their Assay in Differential Diagnosis, *New England J. Med.* 223: 369, 1940.
108. Bauman, E. J., and Metzger, N.: Colorimetric Estimation and Fractionation of Urinary Androgens, *Endocrinology* 27: 664, 1940.
109. Munson, P. L., Gallagher, T. F., and Koch, F. C.: Isolation of Dehydroiso-androsterone Sulfate From Normal Male Urine, *J. Biol. Chem.* (In Press.)
110. Callow, N. H.: Isolation of Two Transformation Products of Testosterone From Urine, *Biochem. J.* 33: 559, 1939.
111. Callow, N. H., and Callow, R. K.: The Isolation of 17-Ketosteroids From the Urine of Normal Women, *Biochem. J.* 33: 931, 1939.
112. Callow, N. H., Callow, R. K., and Emmens, C. W.: The Effect of the Administration of Testosterone Propionate on the Urinary Excretion of Compounds Allied to the Steroid Hormones, *J. Endocrinol.* 1: 99, 1939.

113. Dorfman, R. I., Cook, J. W., and Hamilton, J. B.: Conversion by the Human of Testis Hormone, Testosterone to Urinary Androgen, Androsterone, *J. Biol. Chem.* 133: 753, 1939.
114. Venning, E. H., Hoffman, M. M., and Browne, J. S. L.: Isolation of Androsterone Sulfate, *J. Biol. Chem.* 146: 369, 1942.
115. Callow, N. H., and Callow, R. K.: Excretion of Androgens by Eunuchs; the Isolation of 17-Ketosteroids From the Urine, *Biochem. J.* 34: 276, 1940.
116. Hirschmann, H.: Steroids of Urine of Ovariectomized Women, *J. Biol. Chem.* 136: 483, 1940.
117. Kenyon, A. T., Gallagher, T. F., Peterson, D. H., Dorfman, R. J., and Koch, F. C.: The Urinary Excretion of Androgenic and Estrogenic Substances: Studies in Hypogonadism, Gynecomastia and Virilism, *J. Clin. Investigation* 16: 705, 1937.
118. Hamilton, J. B., Dorfman, R. J., and Hubert, G. R.: Androgenic and Estrogenic Substances in Urine of Eunuchoid and Castrate Men; Changes Following Administration of Testosterone Propionate, *J. Lab. & Clin. Med.* 27: 914, 1942.
119. McCullagh, E. P., and Lilga, H. V.: Bioassays for Urinary Androgens 26: 753, 1940.
120. Fraser, R., Forbes, A. P., Albright, F., Sulkewitch, H. W., and Reifenshtein, E. C., Jr.: Colorimetric Assay of 17-Ketosteroids in the Urine, *J. Clin. Endocrinol.* 1: 234, 1941.
121. Hamblen, E. C., Cuyler, W. K., and Baptist, M.: Urinary Excretion of 17-Ketosteroids in Ovarian Failure. IV. During the Climacteric and After Artificial Menopause, *J. Clin. Endocrinol.* 1: 777, 1941.
122. Callow, R. K.: Isolation of the Male Hormone Present in the Urine of a Patient With an Adrenal Tumor, *Chem. and Ind.* 55: 1030, 1936.
123. Crooke, A. C., and Callow, R. K.: The Differential Diagnosis of Forms of Basophilism (Cushing's Syndrome), Particularly by the Estimation of Urinary Androgens, *Quart. J. Med.* 8: 233, 1938.
124. Wolfe, J. K., Fieser, L. F., and Friedgood, H. B.: The Nature of Androgens in Female Adrenal Tumor Urine, *J. Am. Chem. Soc.* 63: 582, 1941.
125. Dorfman, R. J., and Wilson, H. M., and Peters, J. P.: Differential Diagnosis of Basophilism (Cushing) and Allied Conditions (Cortical Tumors and Arrhenoblastomas), *Endocrinology* 27: 1, 1940.
126. Burrows, H., Cook, J. W., Roe, E. M. F., and Warren, P. L.: Isolation of  $\Delta^{3,5}$ -Androstadiene-17- One From the Urine of a Man With a Malignant Tumor of the Adrenal Cortex, *Biochem. J.* 31: 950, 1937.
127. Talbot, N. B., Butler, A. M., and Berman, R. A.: Adrenal Cortical Hyperplasia With Virilism, *J. Clin. Investigation* 21: 559, 1942.
128. Weil, P., and Browne, J. S. L.: A Cortin-like Action of Extracts of Human Urine, *Am. J. Physiol.* 126: 652, 1939.
129. Selye, H., and Schenker, V.: A Rapid and Sensitive Method for Bioassay of the Adrenal Cortical Hormone, *Proc. Soc. Exper. Biol. & Med.* 39: 518, 1938.
130. Dorfman, R. J., Horwitt, B. N., and Fish, W. R.: The Presence of a Cortin-like Substance (Cold Protecting Material) in the Urine of Normal Men, *Science* 96: 496, 1942.
- Dorfman, R. J., Shipley, R. A., and Horwitt, B. N.: The Presence in Normal Urine of a Cortin-like Material Which Is Active in a Muscle Work Test, *Am. J. Physiol.* 139: 742, 1943.
131. Venning, E. H., Hoffman, M. M., and Browne, J. S. L.: The Life Maintaining Properties of Cortin-like Material Excreted Post-operatively, *J. Biol. Chem.* 148: 455, 1943.
132. Butler, G. C., and Marrian, G. F.: The Isolation of Pregnane-3,17,20-Triol From the Urine of Women Showing the Adreno-genital Syndrome, *J. Biol. Chem.* 119: 565, 1937.
133. Venning, E. H., Weil, P. G., and Browne, J. S. L.: Excretion of Sodium Pregnanediol Glucuronide in the Adrenogenital Syndrome, *J. Biol. Chem.* 128: cvii, 1939.
134. Cuyler, W. K., Ashley, C., and Hamblen, E. C.: Urinary Excretion of Pregnanediol Complex: III. Following Intramuscular Administration of Desoxycorticosterone Acetate, *Endocrinology* 27: 177, 1940.
- Cuyler, W. K., Hoffman, M. M., Kasinen, V. E., and Browne, J. S. L.: The Excretion of Pregnanediol Following the Administration of Desoxycorticosterone Acetate to Rabbits, *J. Biol. Chem.* 147: 259, 1943.
135. Frank, R. T.: A Suggested Test for Functional Cortical Adrenal Tumor, *Proc. Soc. Exper. Biol. & Med.* 31: 1204, 1934.

136. Simpson, S. L., and Joll, C. A.: Feminization in a Male Adult With Carcinoma of the Adrenal Cortex, *Endocrinology* 22: 595, 1938.
137. Crooke, A. C.: Change in Basophile Cells of Pituitary Gland, Common to Conditions Which Exhibit Syndrome Attributed to Basophile Adenoma, *J. Path. & Bact.* 41: 339, 1935.
138. Albright, F., Smith, P. H., and Fraser, R.: A Syndrome Characterized by Primary Ovarian Insufficiency and Decreased Stature. Report of Eleven Cases With a Digression on Hormonal Control of Pubic and Axillary Hair, *Am. J. M. Sc.* 204: 625, 1942.
139. Kepler, E. J., Peters, G. A., and Mason, H. L.: Addison's Disease Associated With Pubic and Axillary Alopecia and Normal Menses, *J. Clin. Endocrinol.* 3: 497, 1943.
140. Varney, R. F., Kenyon, A. T., and Koch, F. C.: An Association of Short Stature, Retarded Sexual Development and High Urinary Gonadotropin Titters in Women, *J. Clin. Endocrinol.* 2: 137, 1942.
141. Scott, W. W., and Vermeulen, C.: Studies on Prostatic Cancer. V. Excretion of 17-Ketosteroids, Estrogens and Gonadotropins Before and After Castration, *J. Clin. Endocrinol.* 2: 450, 1942.

## HORMONAL TUMORS OF THE ADRENAL

GEORGE F. CAHILL, NEW YORK, N. Y.

*(From the Squier Urological Clinic of the Columbia-Presbyterian Hospital  
Medical Center, New York)*

THERE is perhaps no more fascinating study among all tumors than that dealing with the bizarre symptoms of those occurring in the hormonal glands. When tumors appear in which hormones are produced, syndromes occur in the individual due to the effect of the abnormal amount of hormone or hormones elaborated. In certain rare instances perverted hormones may be produced by tumor cells. Among the tumors occurring in the hormonal glands, the adrenal presents as wide a variety as any other in its diversification of symptoms, and in this resembles the pituitary; often the symptoms from dyscrasia of these two glands resemble each other. When tumors occur in the adrenal, they may be either of the cortex or of the medulla, and in either they may produce hormones or they may not.

In 1928, at the Squier Clinic of the Presbyterian Hospital, we became interested in the study of an adrenal cortical tumor and in conjunction with other departments have studied a number of these cases. A review of this study is presented.

Because of a much clearer understanding of the clinical status of the adrenal to its physiologic functions and pathologic changes, the more recent studies of its embryology and biologic processes are interesting.

The mammalian adrenal is actually two glands fused together in development. Each of the glands has an essentially different origin, a different type of tissue, and a separate function. They happen to be enclosed in one enveloping capsule and tissue stroma. The adrenals are normally situated in the outer layer of the renal capsule above each kidney. Recently O'Crowley and Martland have shown that occasionally they may be closely attached to the kidney and rarely may be under the true capsule of the kidney itself. Accessory adrenals occur, are of cortical tissue, and have been called Marchand's bodies. They have been described as of the kidney, the perirenal fascia, the retroperitoneal fascia, within the broad ligament, attached to the ovary, or associated with gonadal testicular tissues. Tumors of these adrenals have occurred, all of the cortical type, and with and without similar syndromes as are seen with adrenal cortical tumors.

## THE ADRENAL CORTEX

The adrenal cortex originates from the mesoderm of the colon epithelium near the genital ridge. The cortex during postnatal life gradually forms into three microscopic layers, which are completed at or about puberty. The development of the inner of these three layers just before puberty has been shown by Miller, Deansley, and Whitehead to have some connection with the development at that time of the sexual glands and organs. Because of increase in size of the layer at this time it was suggested as an X zone of the adrenal. A further elaboration of this suggestion was made by Grollman, who suggested that the inside cells of the inner layer may be androgenic cells, and he described this as an androgenic layer to explain the effects from its suggested function.

A clearer explanation of the development and growth of the adrenal cortex has been furnished by the studies of Bogomoloz, Goormaghligh, Hoerr, and Zwemer, in which they have shown that the adrenal cortex apparently grows continuously during life from without inward. New cells are constantly formed from the spindle-shaped cells under the fibrous capsule, and in their growth develop from without inward the zona glomerulosa, the zona fasciculosa, and the zona reticulosa. During this process they elaborate, accumulate, and discharge lipid sterol and then, degenerating, are absorbed in the reticulosa near the medulla. The elaborated material is discharged into the capillaries by the mature cells before their degeneration, and the process is constant, with replacement by new cells. The removal of the degenerated cells is by macrophages and microphages near the medulla.

There may be hypoaactivity of the process as well as hyperactivity. Under certain phases of hyperactivity, normal or pathologic, there may appear to be larger numbers of cells undergoing degeneration than are normally seen. When this occurs, it may be the reason for the widening of the "reticulate zone at puberty" (Deansley and Miller) or the special zone "androgenic" (Grollman), and the larger number of cells with degenerative fuchsinophilic staining granules as reported by Broster and Vines.

## THE PHYSIOLOGY OF THE ADRENAL CORTEX

The adrenal cortex has been definitely established as the elaborator of hormonal substances, some of which are necessary for life maintenance. These hormonal substances have been shown chemically to be sterol lipoids.

Many closely related sterol derivatives have been prepared from the adrenal cortex. Some have had definite hormonal action. The action of some has effects upon the salt and water metabolism, the electrolyte balance, the permeability of the capillaries, the regulation of the carbohydrate fat and protein metabolism, the renal function, the capacity of muscle response, and the resistance to stress. The maintenance of life

and health is probably due to a combination of the various activities of the steroids. Of the identified steroids, one desoxycorticosterone seems to be most effective in the regulation of the salt and water metabolism, the electrolyte balance, in capillary permeability, and in the preservation of renal function, but it apparently does not include many of the other hormonal functions of the adrenal, particularly that of carbohydrate metabolism.

Another of the identified steroids occurring in the substance of the adrenal cortical cells is one with the property of male hormone (dehydroiso-androsterone). This differs slightly from the testicular male hormone (androsterone), which has also been described as being produced by the adrenal cortex. There has been also identified as secreted by normal adrenals the female hormones, estrone and progesterone. Thus, normal adrenals have the power to elaborate both male and female sex hormones. Part of the hormones occurring in the urine of normal males and females is considered to be derived from the adrenal.

From the multitude of experiments reported, there are many suggestions that the adrenals are implicated in many other metabolic processes. There has been shown that there is a relationship between the adrenal cortex and the pituitary and gonads, and that hyperactivity of the ovary may partially replace adrenal function. It is now suggested clinically that adrenal function may partially replace testicular function. In addition, the adrenal has been suggested as one of the regulators of vitamin balance. It has been shown to have relatively large amounts of vitamin C in its cortical cells.

#### PATHOLOGIC PHYSIOLOGY

Since the adrenal cortex is composed of hormonal secreting cells, there are periods of cell growth or cell degeneration in which hormones are not elaborated. Tumor or hyperplasia of immature cells only will not increase the hormones delivered into the capillaries. Such tumors, when they occur, are nonhormonal. However, hyperplasia or tumor of cells that have matured will elaborate and secrete into the capillaries excess hormones over normal because of the increase of number of cells. The hormones may apparently be of all the steroids, or, as has been suggested by clinicopathologic studies, only excesses of certain hormones may be produced. Such has been shown to be the result of hyperplasia or tumor in the adrenogenital syndrome, in which the excess amount of male hormones elaborated by the tumor has its effect upon the secondary sex organs. This has been shown to occur in the masculinization of females, both children and adults, and in the male maturity of male children.

Other tumors have occurred in which the excess hormone elaborated has female hormonal activity. Thus, Burrows and co-workers and

Simpson and Joll have shown the feminism of a male to be the result of excess estrogens elaborated by a tumor of the adrenal cortex. In earlier reports Cahill, as well as Frank, have shown that high amounts of estrogens occur in the urine of females with adrenal cortical tumors, although the hormonal effect upon these individuals has been that usually produced by excess male hormones.

The syndrome described under many variations as Cushing's has been contended by Bauer to be due to an excess of the adrenal cortical hormones, which have to do with the regulation of the electrolytes, salt and water, and fat and sugar metabolism, and are produced by the adrenal cortex, either in hyperplasia secondary to pituitary effect or in tumor of the adrenal itself. There have been many supporters of this theory, both from experimental and clinical observation.

It has been well established that the adrenal thus can elaborate androgens and estrogens, as well as other metabolic hormonal steroids; that these hormones may be present in excess quantities in hyperplasia and tumor and can be responsible for the symptoms present. There may be produced an increase of normal hormones, and, as has been shown, abnormal hormones may be produced by tumor cells. Such is the conclusion of the report of Butler and Marrian, in which a steroid with male hormonal properties (pregnane 3, 17, 20 triol) was found in the urine in a case of adrenal cortical tumor; they established the fact that such a hormone is not excreted by normal man or from a normal or pregnant woman. The possible finding of other abnormal steroids awaits similar investigation of other cases.

#### CLINICAL CLASSIFICATION OF TUMORS

Since the beginning of our interest in cases of syndromes due to adrenal changes, some with few and others with many symptoms suggesting adrenal pathology, hundreds of cases were studied. From the large number examined and after a serious attempt to prove either the presence or absence of tumor, the conclusion has been drawn that adrenal syndromes may be often due to adrenal pathologic physiology, but they are rarely due to actual tumor. When tumors do occur with hormonal changes, these symptoms vary according to the hormones secreted, their amount, and the age and sex of the individual so afflicted.

On the basis of proved cases, the following clinical groups of adrenal cortical tumors have been previously described (Cahill, Melicow, and Darby):

1. No recognizable hormonal changes
2. Changes due to excess androgens
  - a) In female child toward adult masculinity
  - b) In female adult toward masculinity
  - c) In male child toward adult masculinity

3. Changes due to excess estrogens
  - a) In adult male toward femininity
4. Changes due to excess androgens and other steroids
  - a) Cushing's syndrome with associated sexual changes (mostly in females)
5. Changes due to excess of other steroids related to metabolism
  - a) Cushing's syndrome without sexual changes (in male and female)

#### TUMORS WITH SYMPTOMS DUE TO EXCESS ANDROGENS

*In the Female Child.*—Thomas Cook, in 1765, first described a child with changes undoubtedly due to excess androgens. This was followed by Bevan and Romkild in 1802, Telesius in 1803, Ogle in 1865, and Colcott, Fox, and Ogston. Because of the dramatic changes this type was recorded early. The occurrence in female children is not frequent but forms a fair percentage of the recorded adrenal tumors.

When the disease occurs before birth or in early infancy in the female child, the symptoms have been described as pseudohermaphroditism. Gallais thought that true hermaphroditism could occur if an adrenal cortical tumor was present early in fetal life, but that is no longer held tenable. When pseudohermaphroditism occurs after birth a hypersecretion of the adrenal cortex, whether due to hyperplasia or tumor, may definitely be the cause of the syndrome. In these children all degrees of secondary sex changes are found, from only a slight enlargement of the clitoris to an enormous size like a penis, accompanied by atresia or absence of the vagina. The internal genitals are usually small and sometimes deformed.

From the work of Green, Ivy, and others, it is strongly suggested that the syndrome of pseudohermaphroditism of birth and perhaps early infancy, when not due to definite adrenal hypertrophy or tumor, may be the result of the effect of abnormal hormonal activity of the mother upon the fetus during gestation.

The occurrence of female pseudohermaphroditism is not frequent. Five of these children have been studied for a number of years. Two were seen at 3, one at 4, one at 5, and one at 9 years of age. The condition of all began early in life with the hypertrophy of the clitoris, with the appearance of hair upon the genitals, excessive body growth for a while, increase in musculature, deepening of voice, accelerated epiphyseal and dental development, and a higher mental aptitude than their normal age level. In all, androgens were demonstrated in the urine. Air-insufflation roentgenograms showed the adrenals well in all. Four had apparently a bilateral increase in size. Complete operative explorations showed female internal organs. Biopsies of the ovaries showed no testicular cell inclusions. Section of the adrenals showed an apparent age acceleration in the adrenal zones and cells. None of



the children with these syndromes have shown any evidence of adrenal tumor, and some have been observed for several years. All have had amputation of the penile clitoris. Those who had the adrenals sectioned had the hormonal output apparently temporarily diminished. All have shown marked symptomatic improvement with administration of a potent female hormone.

From the literature these syndromal cases are not uncommon. The causation of these symptoms by tumor is infrequent, but that tumor can be the cause of pseudosexual precocity is amply supported in the report by Reilly, Lisser, and Hinman, in which they cite their case of a child of 22 months with pseudosexual precocity only, due to an adrenal cortical tumor. Microscopically it was a carcinoma of the adrenal cortex. In a compilation of the literature they found forty cases of pseudosexual precocity. Of thirteen patients with pseudosexual precocity alone, two were shown to have tumor, and these tumors were successfully removed. They found three reported cases of successful removal of aberrant adrenal tissue tumors producing the same syndrome. None of these successful cases showed the other symptoms associated with the Cushing syndrome. They found records of ten patients in whom tumors were present with the syndrome, all of whom died either during operation or within three days. Two of these had symptoms of the Cushing type. They recorded fifteen cases without operation, in which adrenal cortical tumors were found on autopsy. In eight of these symptoms suggestive of hormonal influence of the Cushing type were found: obesity, bloatedness, flabbiness, glycosuria, and osteoporosis.

The older children in prepuberty usually do not menstruate, even though the period of puberty has been reached. There have been four recorded cases of menstruation in these children. It is possible that some of these tumors may have secreted estrogens, but as yet no reports of this finding have been recorded.

The older children are more apt to develop a more general hirsutism, on the face and chest as well as the body. Deepening of the voice is often present. There is usually transitory, rapid growth, followed by closure of the epiphyses and a later relative shortness of the individual.

The operative results in these children have been good, considering the seriousness of the hormonal effects. Collett was the first, in 1924, to report a successful removal in a child. Up to 1939, Lisser was able to collect seven successful cases. From the description of the cases, the successful results were among those apparently with only sex syndromes. Among the records of the unsuccessful results have been recorded symptoms suggestive of other metabolic changes. Ten patients dying at operation or within three days suggest that, beside surgical shock, acute adrenal deficiency might have been responsible.

*In Adult Females, Causing Changes Toward Adult Masculinity.*—In the female after puberty and before the menopause, there occurs what has been called the adrenogenital syndrome. According to Wintersteiner, this in its broadest sense comprises all conditions in which the abnormal changes in the sexual sphere are referable to organic or functional disturbances in the adrenal cortex. In these females it consists of the appearance of male secondary sex characteristics and the repression of female characteristics and function. Aspert called it "adrenal virilism." When the syndrome becomes established after puberty or in later life, hirsutism is the first change noted, followed by irregularity or cessation of the menses, changes in the body contour, and enlargement of the clitoris.

This type of syndrome is not infrequent. For the last fifteen years we have examined several hundred females showing some or all of its symptoms. From a study of these cases, the anatomic condition of the adrenal gland has often been found to bear no definite relation to the type or severity of the symptoms. The glands with the syndrome may be often grossly normal, slightly or considerably hyperplastic.

Tumor is not a frequent cause of the syndrome. When an adrenal cortical tumor is present with the syndrome, its complete removal is followed by the cessation of the syndrome with a return, all or in part, toward normal and is now considered to be definitely the cause of the syndrome. When tumor occurs, the first symptom has been scantiness of menstruation followed by cessation. When the menses cease, the cessation has been complete. Frequently headaches may occur at the time when menstruation should have occurred. Associated with the absence of menstruation has been a loss of sexual desire. Transfer of attraction to females has been described with return to normal opposite sex after removal of the tumor. Preceding the cessation of the menses or coincidental with or shortly afterward, there is a marked increase in the growth of hair on the face, chin, and body, all resembling the masculine distribution. Acne often occurs on face and chest. The voice frequently becomes deeper and masculine in tone.

Changes occur in the secondary sex organs, but this change is a slower one than that seen in the hair and menses. The younger the individual, the more pronounced are the secondary sex changes. The usual changes in the sexual organs are hypertrophy of the clitoris, deepening of the color of the labia, atrophy of the uterus, and atrophy and loss of sensitivity of the ovaries. In young females the breasts may stay undeveloped, resembling a boy at puberty. In older women atrophy may occur.

These changes have been shown to be associated with the appearance of excessive amounts of androgens in the urine. The amounts of androgens excreted are proportionate to the masculinity changes that have occurred. The amount may be far above that normally excreted

by males. From one of our cases, Gallagher reported 480 international units per day, and the average value for the normal male in his estimation was 40 international units per day. The highest recorded figure has been in the case described by Slot, in which the excretion reached the astounding figure of 2,200 international units per liter. The male hormone isolated from the urine in some of these tumor cases has been identified as dehydro-iso-androsterone.



Fig. 1.—Case of young woman with apparently only excess of male hormone produced by adrenal cortical tumor. Photograph before operation, showing one day's growth of beard.

There were two patients among the observed adrenal cases in which the only changes caused by the tumor could have been produced by excess androgens. They both had the amount of excretion estimated, the tumor diagnosed, located, and removed, with the disappearance of the male hormone in the urine following the removal of the tumor and the gradual return to normal of their secondary sex characteristics. Both of these cases were reported completely in 1942 (Cahill, Melicow, and Darby). One of these patients later had a reappearance of her syndrome with androgens in the urine, a tumor diagnosed in the opposite adrenal, identified as present by air-insufflation x-rays, and the tumor resected from the normal portion of the adrenal, followed again by the disappearance of the androgens in the urine and the gradual restoration of secondary sexual characteristics to the female.

These two cases presented tumors with secretion of marked excess androgens. The androgens in both produced masculinization, less in the

case with less hormones and marked in the case with excessive excretion. Removal of the tumors in each of these was not accompanied by acute adrenal deficiency, because with only excess androgens secreted there apparently was no functional atrophy of the opposite adrenal in excretion of life maintenance hormones. In one patient with ultimately bilateral tumors, a partial resection was done on each side.

In none of these tumors could a definite diagnosis of carcinoma be made. Pathologically they were thought to be adenoma.



Fig. 2.—Photograph of face taken after operation, with one day's growth of beard.

*Changes in a Male Child Toward Adult Masculinity.*—The usual syndrome described with adrenal cortical tumor in a male child has been that of precocious puberty. In very few cases tumors of the pineal gland have been responsible for sexual precocity in boys (Weinberger and Grant). There have been reported three patients as having the syndrome caused by testicular tumor (Sacchi, Moreau, and Parkes-Weber and Howland). A number of cases have been described in the literature as due to no known cause. Among these has been a description of its familial tendency without tumor by Rush, Bilderback, Slocum, and Rogers under the term *macrogenitosoma*. The occurrence of the syndrome as caused by adrenal cortical tumor is not frequent. Kepler states its frequency as twelve times among thirty-seven known adrenal tumors in children, a proportion of about two females with *pseudopubertas praecox* to one male with *pubertas praecox*.

Among the earlier cases was that reported by Linser, in 1903, of a boy 5 years of age with a left adrenal tumor with metastases. The sec-

ond was Adams, in 1905. Player and Lissner added one to the literature up to 1932, bringing the total to nine.

Cases of the syndrome must occur without reporting, either because of the marked advance of the disease before recognition, so that no operative procedure was undertaken, or because no autopsy was possible to prove the diagnosis. Broster and associates, in an exhaustive study of cases, recorded only one case of a male with prematurity. Fraser reported a case in 1941 in a child 1 year of age. From the few cases reported, the occurrence of premature puberty caused by adrenal tumor is among the rarer of adrenal tumor cases.



Fig. 3.—Photograph of woman with tumor producing male hormone and other metabolic hormones producing the Cushing-type syndrome.

We have studied five male children with prematurity, 5, 6, 8, 11, and 11 years of age. They all had hair on genitals and body, beginning on the face, and enlargement of the penis. The testes in the younger patients were not enlarged more than the normal age growth. The younger children showed more advanced age growth, advanced dentition, and epiphyseal development. They had no adiposity or other metabolic changes. There were no changes in sella, no evidence of pineal enlargement, and no changes in the thymus. One patient only showed an anatomic enlargement of one adrenal, the left, but this was not confirmed by operation.

The two older boys, 11 years of age, showed marked hirsutism of face and body and marked hypertrophy of the genitals, including the testes. Their symptoms had been present, one for eight and the other for seven years. There was shortening of the stature with fusion of epiphyses. Both had prostatic secretion and sperm. One had normal-sized adrenals by air-insufflation x-rays, and the other had an increase in size of the right adrenal. No operative procedures were done. These cases resembled the description of familial pubertas praecox described by Rush and associates.

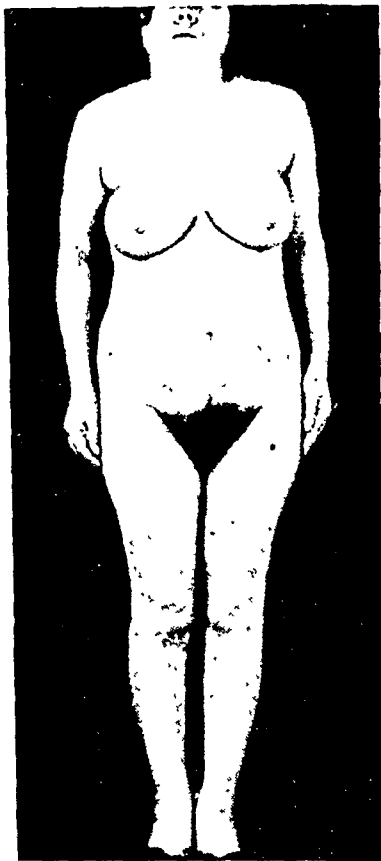


Fig. 4.—Photograph of woman with tumor producing only changes of metabolic hormones of the Cushing type. No female or male hormone was identified as excreted in her urine.

A case was seen in the terminal stage of a child of 5 years of age, with all the symptoms of the syndrome. This patient showed the facial and neck obesity as well as body obesity and genital hypertrophy described as the infant Hercules type. He had a large abdominal tumor, presumably adrenal. No pathologic specimen was obtainable.

The operative results reported on the few boys with the syndrome have had a very high mortality. In addition to the prematurity,

most obviously due to the effect of androgens, there appears very frequently symptoms suggestive of the changes seen with Cushing's syndrome and with probably a resulting functional atrophy of the opposite adrenal. In Fordyce and Evans' case, practically no adrenal tissue was found at autopsy on the opposite side. Player and Lisser's patient, who made the first surgical recovery in this group, showed only the androgenic effect in his masculine maturity and in his epiphyseal growth. He showed no evidence of acute adrenal deficiency following the removal of the tumor and made an uneventful recovery.

#### TUMORS WITH EXCESS ESTROGENS

Tumors with excess estrogens apparently are the rarest of all the hormonal tumors of the adrenal, only six definite cases of tumors with excess estrogens producing changes in the adult male toward femininity having been reported. The first was by Bittorf in 1919, a male, 26 years of age, who noticed decrease in the size of his testes and enlargement of his breasts. He became impotent and developed a tumor in the left side of his abdomen. Cachexia and death followed, and autopsy (Matthias) showed a "malignant adrenal cortical hypernephrome." Zum Busch reported a similar case with secretion from the patient's breasts and the cause verified by autopsy. Holl reported a patient, 15 years old, who was operated upon, the diagnosis established, but the tumor impossible to remove. He reported a second patient, 44 years old, with similar symptoms in which the tumor was removed by operation, followed by recovery. Following recovery there was a subsidence of breasts, adiposity, and return of sex function. Lisser published autopsy findings of a male, 33 years of age, with breast enlargement and secretion and adrenal cortical carcinoma. Simpson and Joll, in 1938, published an exhaustive investigation of a patient, aged 34 years, who had feminization due to an adrenal carcinoma and excreted an excess of estrogenic hormone (probably estrone). The excess of hormone disappeared after the operation and returned with the recurrence of the tumor in the form of metastases.

We have had one case, a man, aged 53 years, with gain in weight, increase in size of breasts, and changing of his hair to a finer, silkier type. He noticed a complete loss of desire and libido, with marked decrease in size of penis and testes. Perirenal air-insufflation x-rays showed a very large left adrenal. He permitted no further studies, and adrenal tumor was not verified, no operative procedure being done.

From the few cases in the literature and especially from the one reported by Simpson and Joll, the adrenal in these cases was directly responsible for the feminization and the adrenal cells were apparently the source of the estrogenic hormone. It was also shown by Simpson and Joll that androgens were still excreted by their patient.

Of the two reported patients with estrogenic tumors who recovered, in neither was removal of the tumor followed by acute adrenal deficiency.

#### TUMORS WITH SYMPTOMS DUE TO EXCESS ANDROGENS AND OTHER HORMONES

From a study of the literature, tumors with symptoms due to excess androgens and other hormones seem to occur more frequently than any other. The symptoms without the cause being tumor are not infrequent. In the large number of supposed adrenal cases referred to us, this type of adrenogenital syndrome was frequent. Our studies of these showed that a fair number of these patients had hypertrophy of one or both adrenals. Few, however, had tumors as causation.

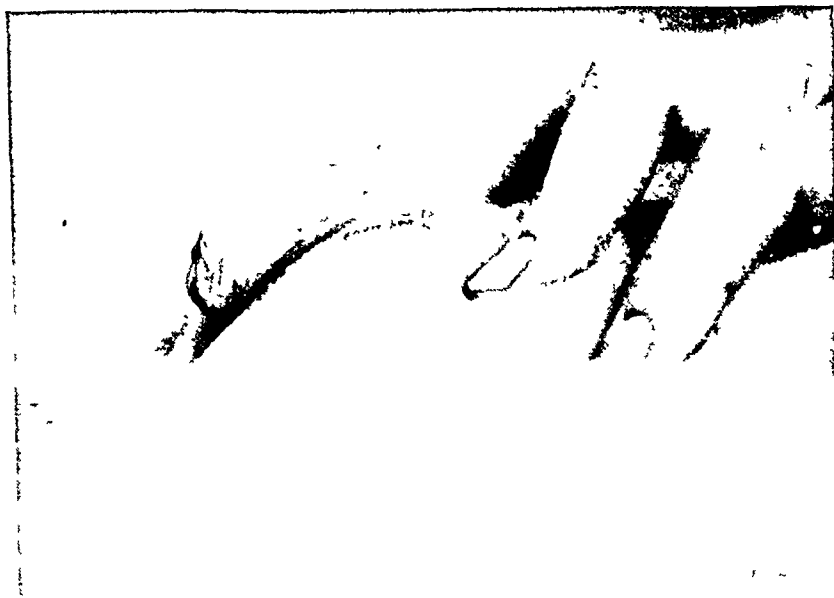


Fig 5.—Hypertrophy of the clitoris in female child with masculine stature due to excess androgens elaborated by adrenal adenoma.

The syndrome as described by Cushing was followed with the suggestion that it occurred with basophilic adenoma of the pituitary. He outlined a clinical picture consisting of a rapid, plethoric, painful obesity, affecting primarily the face, neck, and abdomen, but usually sparing the limbs, thus giving rise to an obesity described as the "buffalo type." The facial changes made the eyes appear small and slitlike, resembling a pig's eye. There was acrocyanosis, with purplish, linear atrophiae on the lower abdomen and the thighs. Hirsutes were marked. There was a tendency toward polycythemia and hypertension, and glycosuria was of frequent occurrence, as were high cholesterol readings. With the syndrome were muscular weakness and porosis of



the bones, causing a cervicodorsal stoop and a shortening of the stature. This latter is rare in adrenal tumors, but more frequent with the pituitary cases. Amenorrhea was present in the females and impotence in the males. There was a marked susceptibility to infectious processes and to physical stress. Mental changes were present, and, in some, well-developed psychoses occurred.



Fig. 6.—Air-insufflated x-ray of young woman with only masculine syndrome. An ovoid tumor of left adrenal is outlined above the kidney.

Since the description by Cushing, many reports have been issued as to the findings in these cases in which opinions have varied as to the causation. Some (Pardee) believe it mostly pituitary. Others reported that it was more frequently associated with adrenal changes (Oppenheimer and Silver, etc.). Some similar syndromes have been reported as having been associated with thymic tumors. A few rare cases with obesity and hirsutes, as well as hypertension, have occurred with the arrhenoblastomas described by Robert Meyer.

From a study of these cases, some of the changes could be due to the effects of excess androgens. These changes were the hirsutes, amenorrhea, and changes in the secondary sex organs, as the breasts and the clitoris. Some patients had these changes to a marked degree and others less. The fat deposits, the skin, polycythemia, hypertension, and glycosuria, as well as the weakness and osteoporosis, can best be explained by excess hormones present, disorganizing such metabolic processes. Bauer

called attention to the fact that these, in their main effects, were the opposite to Addison's disease, and that most of these individuals were suffering from an excess of metabolism steroids produced by the adrenal, either by itself or through stimulation of the pituitary. Considerable support to this has been offered by clinical observers and by investigators.

Tumor of the adrenal has definitely been shown to be a producer of most of the changes in this syndrome. When tumor occurs, the cases may vary from those with marked sex changes and mild other metabolic changes to those with less marked sexual changes and most of those described by Cushing.



Fig. 7—Photograph of tumor removed from patient shown in Fig. 6

We studied and reported three cases (Cahill, Melicow, and Darby) showing these variations. The first, a woman, aged 36 years, had hirsutism, amenorrhea, stoutness, nervousness, and weakness. There was hypertrophy of the clitoris and a mild erythrocytosis. Air-insufflation x-rays of the adrenal showed a large tumor of the right with a small opposite adrenal. She excreted 69 international units of male hormones each day. The right adrenal tumor was removed successfully. Following this removal she developed acute adrenal deficiency and died thirty-six hours later. The second case, a woman, aged 36 years, had weakness, headaches, hirsutes, amenorrhea, edema, acne, erythrocytosis, low sugar tolerance, and hypertension. A larger tumor of the adrenal was shown by perirenal air insufflation. Removal of this by operation was followed by acute adrenal deficiency, but she recovered with

vigorous therapy. After recovery her normal female characteristics returned, only to be replaced again later by masculinization and more marked other metabolic changes with growth of metastases, from which she died. The third woman, aged forty years, had hirsutes, fat on face and body, emaciation of limbs, and amenorrhea. Study showed erythrocytosis, low sugar tolerance, and hypertension. She developed cervicodorsal stoop. Air-insufflation x-rays showed a large tumor of the adrenal. No operation was performed, and follow-up was impossible.



Fig. 8.—Air-insufflation x-ray showing tumor of lower pole of the right adrenal in a patient with only masculinizing syndrome.

The three cases studied appear to be illustrative of the variations caused by the effect of different hormones. The first had well-marked effects of excess androgens and moderate other metabolic disturbances. The second had well-marked sexual changes and other metabolic changes. The last had moderate sexual changes and marked general metabolic changes. In these the demonstration of the tumors by air insufflation was less clearly defined, as the patient developed fatty deposits and edema. The operative results show that apparently, with the excess of metabolic hormones produced by the tumor, hypofunction and atrophy occur in the opposite adrenal. This fact has been reported by other observers. Often when one of these patients recovers it may be due to the excretion of hormones by metastases.

TUMORS WITH CHANGES DUE TO EXCESS OTHER STEROIDS  
RELATED TO METABOLISM

We had one patient previously reported who had all the symptoms described by Cushing with the only real change in the sexual characteristics being the cessation of menstruation. No male or female hormones could be identified as excreted in her urine. A complete autopsy was done after she died with acute adrenal deficiency after removal of the adrenal tumor; this did not reveal any other change that could have produced the syndrome except the adrenal tumor. The remaining

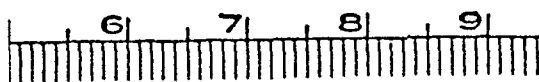


Fig. 9.—Photograph of tumor removed from patient in Fig. 8.

adrenal was atrophic and apparently inactive. In retrospect the tumor must have produced steroids in abundance, as was evidenced by the histologic sections, in which most of the cells were foamy with lipoids. These steroids were neither of androgenic nor estrogenic influence, as was shown by the symptoms and by the failure to identify either in the urine. From her symptoms and the fact that acute death followed the removal of the tumor, the steroids apparently had to do with the life maintenance properties of the adrenal.

THE DIAGNOSIS OF ADRENAL CORTICAL TUMORS  
WITH HORMONAL EXCRETION

From a study of many cases with syndromes suggestive of adrenal changes, only rarely have we found tumor as the cause. When tumor

occurs the symptoms are usually pronounced. If of androgenic character, the identification of large amounts of androgens in the urine is necessary. This is now possible by the estimation of the 17 ketosteroids by the colorimetric method. If the symptoms are of estrogenic character, the estimation of the urinary estrogens biologically is not difficult. Once these excesses are determined, the origin of the hormones is then sought. For the adrenals we have used x-ray studies of air insufflated into the perirenal fascial spaces. These have been reported by us and



Fig 10.—Air-insufflation x-ray showing tumor of the right adrenal resting against the liver in a patient with masculine syndrome and Cushing syndrome.

others. When tumor is present, it is more clearly shown in thin people. The tumors are round when small, ovoid when large, and may be somewhat lobulated when very large. All tumors so diagnosed were confirmed by operation. The air insufflation was especially of value when the tumor was small and unrecognizable by any other method except by operation.

#### THE HORMONES EXCRETED BY ADRENAL CORTICAL TUMORS

*Androgens.*—It is apparently established that virilism and adrenal cortical tumors, when present, are associated with high levels of androgen, and this declines to lower levels after removal of the tumor. The most frequent androgen that has been isolated has been shown to be dehydro-iso-androsterone, a beta-kesteroid. This differs from the hormone of the testes, testosterone, an alpha-kesteroid. It is also thought

that the adrenal may also produce some alpha-kesteroids. Under certain conditions the beta-kesteroids are greatly increased in quantity, as in patients with hyperplasia, adenoma, and carcinoma of the adrenal cortex. In these cases there appears to be a rather definite relation of the amounts of androgens present in the urine to the degree of virilism. The more marked the symptoms, the higher the assay.

It has been shown that at least with one tumor another kesteroid (pregnane) was isolated from the urine by Butler and Marrian and appeared to be associated particularly with that tumor; it was not found in the urine of either normal males or females or of pregnant females. From their finding it appears as if in other tumor cases abnormal or perverted hormones may be elaborated.

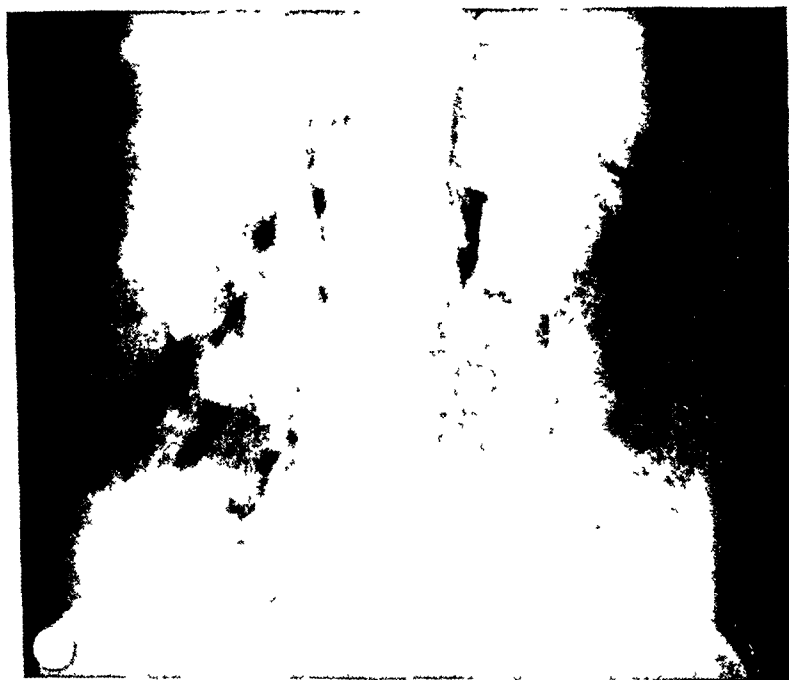


Fig. 11—An-insufflation x-ray showing tumor of the left adrenal in a case of only metabolic changes of Cushing type. The air diffuses poorly around this adrenal due to fatty edema of the tissues

*Esterogens.*—It was shown early that large amounts of estrogens were excreted in the urine of patients with virilism and tumor. In some a definite excess over normal was found, even though the effect on the patient was masculinization. At that time the amount of androgens was unknown. Later we have shown, as well as others, that even though the androgen level is greatly in excess of normal, high estrogen excretions continue in women with adrenal cortical tumors with masculinizing syndromes; and these estrogens remain unchanged after the tumor is removed.

The report of Simpson and Joll confirmed the clinical suspicion that feminizing tumors in males must be associated with high estrogen levels. Their case showed high levels before operation, lowering to normal after removal of the tumor and resumption of high levels again with the reappearance of tumor in the form of metastasis. The estrogens excreted in their case were considered to be estrone.

#### OTHER HORMONES

The identification of other hormones with adrenal cortical tumors awaits further investigation. An increase in substance which maintains life was demonstrated in the blood stream of a patient with Cushing's syndrome. The identification of life-maintaining substances in the urine

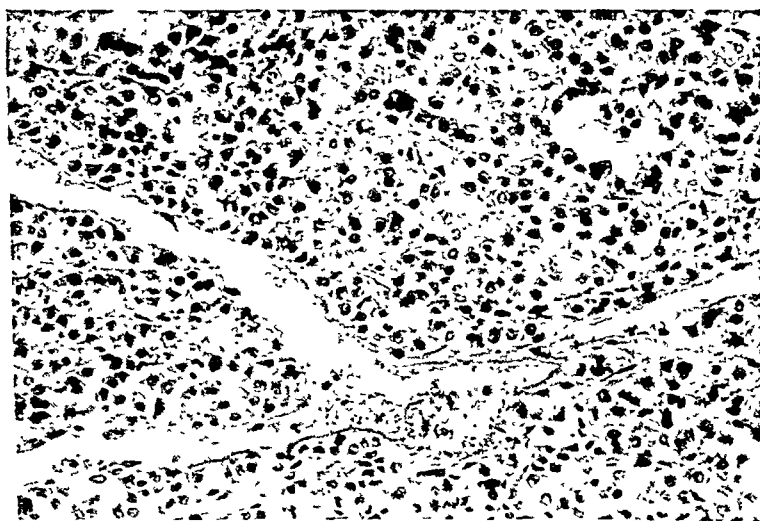


Fig. 12.—Photomicrograph of tumor of adrenal cortex with only masculinizing syndromes.

in normal persons and their increase in stress has been studied by Weil and Browne. Similar investigation into the effects of the Cushing syndrome types is needed. Of particular interest is the patient with Cushing's syndrome, in whose urine no estrogens nor estrogens could be identified.

#### OPERATIVE PROCEDURES

For removal of adrenal cortical tumors, three routes have been used: (1) extraperitoneally through the lumbar region, (2) transthoracically through the chest, and (3) transabdominally through the anterior abdominal wall.

The lumbar route has been used exclusively for removal of adrenal tumors. It did not involve tumor removal. Crile described the method in his approach. Walters and Kepler report on the lateral approach.

determine, first, the diseased side, and, second, the presence of an opposite adrenal. Young devised an ingenious retractor fashioned after a rib-spreader retractor for thoracic procedures and used this retractor for bilateral exposure.

The transthoracic approach was reported by Broster and Vines as useful in cases of nontumor adrenogenital syndrome. This, he claimed, was the easiest approach in view of the fact that the adrenal vessels allowed a slight range of upward movement. It had, however, the disadvantage of creating at times a pneumothorax. He also did a preliminary laparotomy for exploration of the adrenals by palpation, then after recovery performed the main operation by the transthoracic approach.

The transperitoneal approach has been used in association with a bridge elevation similar to gall bladder procedures. This approach we have recommended for cortical tumors because we have felt that,

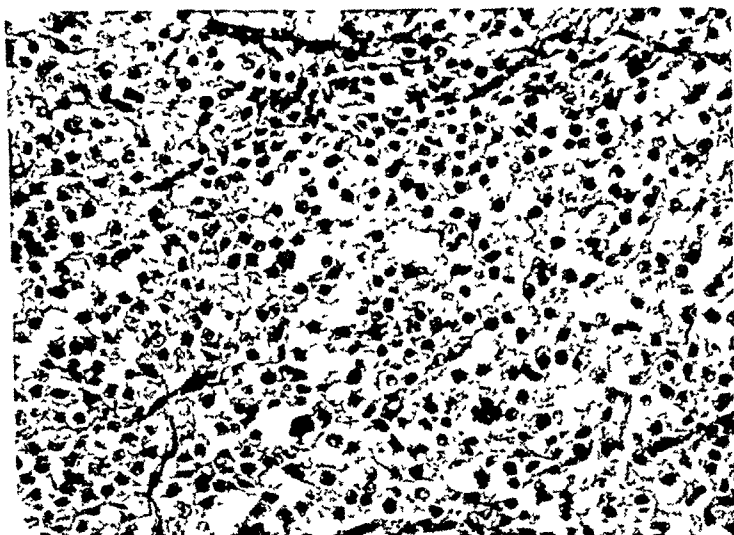


Fig 13—Photomicrograph of tumor of adrenal cortex with mixed syndromes The cells contain many vacuoles of steroids

with the adrenal, in both the lumbar and transthoracic routes the operator was too handicapped with the inadequacy of the incision, the difficulty of first approaching the vessels of the tumor and of ligating them, and the difficulty of manipulating the tumor. The anterior oblique incision gives a large opening, adequate exposure, exploration of the entire abdomen, proper localization of the structures, accessibility to the tumor which always grows down and anteriorly in the direction of the incision, and ability to ligate the vessels before handling the tumor, a most recommended step in dealing with carcinoma and facilitated by far better control of any operative accident. In our series there have been no weaknesses in the abdominal wall subsequent to the operation.



## POSTOPERATIVE ACUTE ADRENAL DEFICIENCY

In the literature many patients are reported with what has been described as shock, occurring immediately or shortly following the removal of an adrenal tumor. Cecil stated that 39 per cent died of this shock and that 65 per cent had severe shock, from which only 27 per cent of all patients operated upon recovered. The other 33 per cent apparently had no shock.

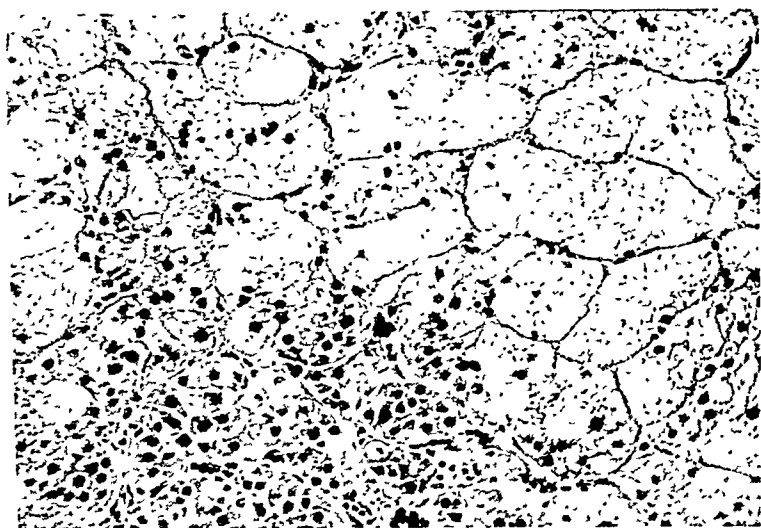


Fig. 14 —Photomicrograph of tumor of adrenal cortex with only metabolic syndromes of Cushing type. Most of the cells are filled with vacuoles.

It is now accepted by most clinicians and investigators that the collapse is characteristic of acute adrenal deficiency. From a perusal of the literature and from our own experience, the acute adrenal deficiency is rare or does not occur in the nonhormonal adrenal cortical tumor cases, nor does it occur in those with only sex hormonal changes, but it occurs most often in those who show the effects of excess hormonal action upon many metabolic factors, the electrolytes, the water and salt balance, and the capillary permeability, in fact, the symptoms seen in the Cushing type of syndrome, whether in children or adults. It has been suggested upon reasonable grounds that these changes can only be produced by excess hormones. Experimentally it has been shown that injections of excess life-maintenance substance can cause atrophy of the adrenals. In those cases ending fatally, usually of the Cushing type of tumor, contra-adrenal atrophy usually is present. Cushing type tumors have been removed, and the patient has recovered from the following acute adrenal deficiency, but often metastases were later recognized; it is thought that their secretion was responsible for the recovery.

The most important factor in surgical therapy in these metabolic-type tumors is the anticipation, prevention, and control of postoperative cortical deficiency. The method used is that with acute crisis of Addison's disease, having on hand and administering preoperatively and postoperatively potent adrenal hormone. A potent extract of the cortex may be used or the synthetic hormone desoxycorticosterone. Adequate doses are given. In addition to the hormone there is administered by oral or parenteral route adequate amounts of sodium chloride and sodium citrate. Since the marked cases of Cushing syndrome have an erythrocythemia, with apparently a marked diminished blood volume, postoperative transfusions are often necessary. Certain students of the syndrome suggest that a diet low in potassium might be of value for some time preceding the operation.

If the patient is tided over the acute deficiency, it is expected that the remaining adrenal tissue will regain its capacity to produce a sufficient amount of hormone to meet the needs of the body. There apparently is no known method to determine the duration of this period, but it probably is safer to err on the side of extension of the therapy for some time after the blood pressure and electrolyte balance have reached normal.

#### PATHOLOGY

The tumors were either adenoma or carcinoma. The adenomas were soft, encapsulated, red tumors. The small ones blended into normal adrenal tissue. With larger ones, no normal tissue was found. The adenomas were more frequent in the younger adults. The cells were typical active adrenal cells, undistinguishable as coming from any particular zone. They at times had granules but contained lipid vacuoles in many cells. The number of cells containing vacuoles compared roughly with the degree of hormonal changes, particularly if the Cushing type of syndrome was present; in this latter the sections of the slides showed that most of the tumors were composed of "foam cells."

The carcinomas varied. These were seen more often in the older cases. None of the carcinomas resembled those seen in adrenal tumors without hormonal syndromes. One carcinoma showed invasion of the capsule and cells in the blood vessels. The cells were in sheets resembling some parts of the adrenal cortex, more frequently the glomerular and reticulate layers. Numerous vacuoles were present. Others had cells mostly undifferentiated with many mitoses and numerous vacuoles.

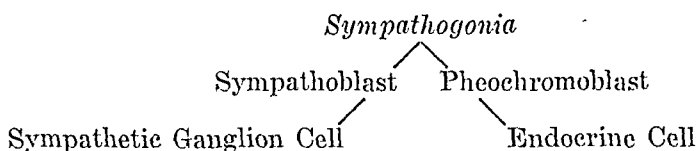
The attempts to correlate the findings of fuchsinophile granules as described by Broster and Vines have still left us unable to decide whether their presence has or has not any particular association with the various types of cases. Fuchsinophile staining of the cytoplasm was present in all the tumors, in some diffusely and in others in gran-

ules. It apparently was more pronounced in cases with hormonal syndromes and in the older individuals. The latter is in accord with Sudds' report that granules appear in adrenal cells, apparently with the ageing process of the individual.

#### HORMONAL TUMORS OF THE ADRENAL MEDULLA

Tumors of the adrenal medulla may be divided clinically into those which produce no hormones and those which do. The latter are rare.

The medulla of the adrenal is of the sympathetic nerve system. The cells are formed from the sympathogonia which grow into the cavity of the adrenal cortex, which gradually extends over the medulla to enclose the same. The primitive sympathetic cell (sympathogonia) forms two types of cells, one the fibril ganglion cell, and the other the secreting endocrine cell. The former, the sympathoblast, forms the mature sympathetic ganglion cell, and the latter, the pheochromoblast, forms the mature pheochromocyte.



The pheochromocyte cell is the mature and apparently only endocrine secreting cell of the adrenal medulla. Long before the present knowledge of its function was known, it had been shown to possess an affinity to chrome salts which stained material in its cells a deep brown. Cells with similar staining properties (chromaffin tissue) occur in the retroperitoneal tissues, sympathetic glands along the aorta, Zuckerkandl's organ, the sacrococcygeal region body, and the carotid body.

The only known secretion of the pheochrome cell is epinephrine. This was the first hormone identified, isolated, and synthesized. Its properties as a pressure substance have long been recognized.

When there is an abnormal number of pheochrome cells produced, as in tumor, the formation of such has been called paraganglioma chromaffinoma, or, more properly, pheochromocytoma. The symptoms of paroxysmal hypertension now known to be associated with pheochromocytoma were first described, in 1922, by Labbé and Tinel-Doumer. The diagnosis as to its causation was made, in 1926, by Vaquez and Donzelot. C. H. Mayo reported, in 1927, the first pheochromocytoma removed during an abdominal exploration. In 1929, Pincoffs reported the first case correctly diagnosed and the patient operated upon. The association of the pressor substance in the blood with the attacks was first reported, in 1937, by Beer, King, and Prinzmetal.

When pheochromocytoma occurs, it is more frequent in the medulla of the adrenal gland, but it may occur next in frequency in the retro-

peritoneal tissue, in the ganglia with the aorta or vena cava, in the sacrococcygeal body, or in the carotid body. When the tumors are small, they are usually soft, reddish tumors with a thin capsule, and usually the adrenal cortex is a yellow rim attached to the tumor. When larger, they become grayish or darker brown. They are vascular and easily ruptured. Hemorrhage and degeneration are not infrequent. Cyst formation may occur.

When the tumor occurs, a symptom complex is seen, which gives rise to what has been described as paroxysmal hypertension. The course has been accepted as being the effect of a release of an excess amount of pressor substances in the blood.



Fig. 15.—Air-insufflation x-ray of patient with pheochromocytoma of the right adrenal.

The tumors so far occur usually in young or middle adult life and in both sexes, although they apparently are more frequent in the female. They are more often benign, and the patient in the rare malignant case may succumb before many metastases occur.

#### THE SYNDROME

The symptoms that occur have been described as paroxysmal hypertension. These may occur spontaneously or may be induced. When they occur they usually are similar each time.

The patient notices that after exercise or mental excitement a marked pounding headache occurs, with the consciousness of the heart beating; that there is tingling of hands and feet with a feeling of constriction of the same and creepy feelings; that palpitation becomes more marked; that dyspnea may occur with nausea or vomiting; and that at

times epigastric pain is marked. An impending sense of death not infrequently occurs. The attacks last from a few minutes to several hours, and in that time the patient may simulate a state of shock. The attacks terminate slowly with flushing of the blanched areas, marked sweating and weakness, and often exhaustion. Death may occur during an attack, from shock, heart failure, coronary disease, cerebral accident, or pulmonary edema. Frequent occurrence of the syndrome may result in arterial changes, in which a more or less continuous hypertension may exist with vascular changes in the eyes.



Fig. 16.—Air-insufflation x-ray of patient with small pheochromocytoma of the lower pole of right adrenal.

#### CAUSATION OF ATTACKS

The attacks may be produced spontaneously or by physical or mental effort. They have been variously described, often being attributed to other causes. Any mechanism that is known to release adrenalin normally from the adrenal may produce the attack, as effort, trauma, anger, fear, exposure to cold or sudden heat, abdominal pressure, massage of the tumor, or, accidentally, administration of a pressure substance. Some patients have awakened from sleep with an attack, probably from dreaming. Not uncommonly, as in several of our cases, the sudden demise in an unrecognized tumor followed by an autopsy discloses the cause.

## VASOCONSTRICTION

The vasoconstriction of the peripheral circulation is usually marked. The blood pressure between attacks may be low or normal. During the attack it may rise to over 300 mg. systolic with a diastolic over 100 mg. of mercury. The pulse is thin and may not be perceptible. The fingers and toes become blanched, as well as the lips and also the fundus oculi. There occurs a difference of pressure reading in the proximal arteries from the distal arteries. Readings by oscillograph may not be possible in the extremities. During this period the pulse is rapid, and the heart pounding may be pronounced.

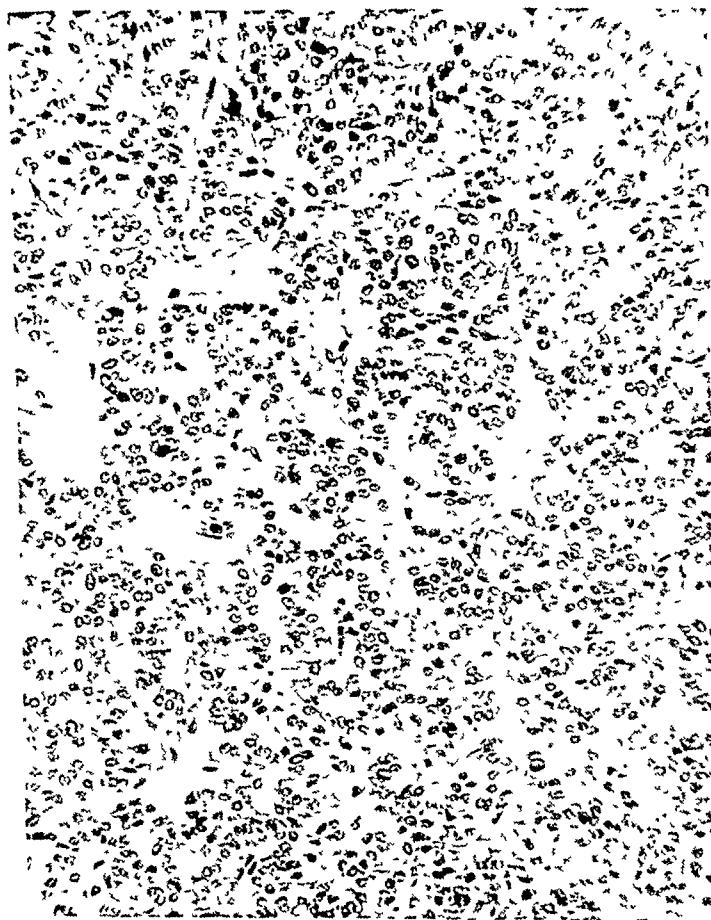


Fig 17—Photomicrograph of pheochromocytoma taken from patient shown in Fig. 15.

*Temperature.*—There is a marked diminution of the peripheral temperature of the body with a rise of the internal temperature. This persists through the attack, evidently produced by inadequate dissipation of body heat. Following the attack, subnormal temperature may be present for a while.

*Shock.*—Following a severe attack or one which has existed a long time, a state of shock may occur. Similar phenomena have been re-

CASE 3 (P. H. No. 438208).—S. P., a woman aged 53 years, was admitted in 1934; she had had so-called attacks of chronic indigestion for years. These were severe with epigastric pain, nausea, vomiting, and often collapse. The attack which brought her to the hospital was the most severe that she had ever had. A presumptive diagnosis of visceral perforation was made. Operation disclosed severe intraperitoneal hemorrhage from a mass above the right kidney. Attempts to control the hemorrhage were difficult, and the patient collapsed and expired. Autopsy showed that the hemorrhage was from a large, benign pheochromocytoma of the right adrenal, and death followed the attempts to control the hemorrhage.

CASE 4 (P. H. No. 542008).—D. P., a female, aged 27 years, was admitted in 1938; she had had a rheumatic heart for years and attacks of abdominal distress and palpitation. She had had an unsuccessful laparotomy eight years previously. She showed a typical syndrome of paroxysmal hypertension and had a palpable tumor mass in the left hypochondrium. Palpation and massage of the tumor mass produced the typical attacks. A partial removal of the tumor, which was attached to the cava and aorta, was followed by collapse and death. Autopsy showed severe rheumatic endocardial changes, marked arteriosclerosis, and a pathologically benign pheochromocytoma of the left aortic lumbar plexus.

CASE 5 (Neurological Institute No. 41024).—G. K., a man aged 61 years, was admitted in 1939. He had evidence of personality changes and had convulsive attacks. A diagnosis of brain tumor was made, and at operation a tumor was removed. Five days following the operation he died in a sudden collapse. Autopsy showed severe intraperitoneal hemorrhage from a pheochromocytoma of the right adrenal. The tumor removed from the meninges was diagnosed on microscopic examination as pheochromocytoma. There were no other metastases found.

CASE 6 (P. H. No. 600888).—E. C., a woman aged 49 years, was admitted in 1940 with a history of the typical syndrome of pheochromocytoma. The tumor was localized as in the right adrenal by air-insufflation x-rays. She was operated upon, the tumor removed from the adjacent cortex, and she made an excellent recovery and has been well since. The tumor was a benign pheochromocytoma.

CASE 7 (P. H. No. 657128).—J. S., a woman aged 48 years, was admitted in 1941 with hirsutism, obesity, and amenorrhea which had been present for years. One year before, the left adrenal had been explored in another hospital with no tumor found and the symptoms persisting unchanged. A tumor of the right adrenal was shown by air-insufflation x-rays. The tumor was removed by resection from the cortical portion because of symptoms of adrenogenital syndrome and because of the uncertainty of the status of the left adrenal after the previous operation. The tumor was shown microscopically to be a benign pheochromocytoma, but a removed portion of the cortex showed adrenal hyperplasia with many foam cells seen often with the Cushing type. An acute cortical adrenal deficiency following was treated by cortical hormone and she recovered. The patient has been free from the hypertension syndrome since the operation.

CASE 8 (P. H. No. 690134).—E. R., a female, aged 29 years, was admitted in 1942. For one year she had had attacks of paroxysmal hypertension. Studies did not reveal any changes in the adrenal, but there was a tumor mass below and mesial to the right kidney. Operation disclosed a tumor of the right aortic lumbar plexus. The tumor was removed. It was a benign pheochromocytoma. There has been no recurrence of the syndrome since operation.

CASE 9 (P. H. No. 623060).—H. A., a female, aged 25 years, was admitted in 1943, with hirsutism, mild obesity, and scanty menses. For one year she had had

typical syndromal attacks of paroxysmal hypertension. Insufflation x-rays showed a small bulbous mass at the lower pole of the right adrenal similar to that in Case 6. She refused operative intervention.

These nine cases cover the historical study of these tumors: The early case with an entirely unrecognized syndrome; the marked tendency of these tumors, particularly the right, to bleed intraperitoneally; the collapse and death that may occur with any traumatism; with hemorrhage from the gland, and with operative handling; the later recognition of the syndrome, with proper diagnosis, proper localization of the tumor, and its successful removal. Of the nine tumors, two metastasized and were thus presumed to be malignant.

#### SUMMARY

##### *Cortical Hormonal Tumors.—*

1. The hormonal syndromes may be due to an excess of androgens or estrogens or other metabolic hormones of the cortex.
2. The syndromes are determined by the type and amount of hormone or hormones produced and by the age and sex of the patient.
3. The status of the adrenals may be adequately determined by air-insufflation x-ray pictures.
4. Removal of the tumor, if adenoma, will cure the syndrome, but often fixed changes will persist. If the tumor is carcinomatus, its removal may temporarily improve the patient.
5. Acute adrenal deficiency occurs usually in those with symptoms of the Cushing syndrome, and the treatment is that of acute deficiency in Addison's disease.

##### *Medullary Hormonal Tumors.—*

1. The hormonal syndromes are due to an excess of epinephrine.
2. The cases vary only in degree with the amount of the hormone produced.
3. The diagnosis is made upon:
  - (a) a typical syndrome and response
  - (b) demonstration of a pressure substance
  - (c) the presence of tumor by air-insufflation x-ray pictures
4. The danger period is during the operation, although at times acute adrenal deficiency may develop from removal of cortical tissue.
5. If patients survive the operative period, the prognosis is good, because most of the tumors are benign.

#### REFERENCES

##### *Cortical Hormonal Tumors*

1. Apert, E.: Bull. Soc. pédiat. de Paris 12: 501, 1910.
2. Bauer, J.: Klin. Wehnschr. 12: 1553, 1933.
3. Beer, E., King, F., and Prinzmetal, M.: Ann. Surg. 106: 85, 1937.
4. Bittorf, A.: Klin. Wehnschr. 56: 776, 1919.



5. Bogmoloz, A.: *Folia serolog.* 3: 125, 1919.
6. Broster, L. R., Allen, C., Vines, H. W. C., Patterson, J., Greenwood, A. W., Marrian, G. F., and Butler, G. C.: *The Adrenal Cortex and Intersexuality*, London, 1938, Chapman & Hall, Ltd.
7. Broster, L. R., and Vines, H. W. C.: *The Adrenal Cortex*, London, 1933, H. K. Lewis & Co., Ltd.
8. Burrows, H., Cook, J. W., Roe, E. M. F., and Warren, F. L.: *Biochem. J.* 31: 950, 1937.
9. Butler, G. C., and Marrian, G. F.: *J. Biol. Chem.* 119: 565, 1937.
10. Cahill, G. F.: *J. Urol.* 34: 238, 1935.
11. Cahill, G. F., Loeb, R. F., Kurzrok, R., Stout, A. P., and Smith, F. M.: *Surg., Gynec. & Obst.* 62: 287, 1936.
12. Cahill, G. F., Melicow, M. M., and Darby, H. H.: *Surg., Gynec. & Obst.* 74: 281, 1942.
13. Cecil, H. L.: *J. A. M. A.* 100: 463, 1933.
14. Collett, A.: *Am. J. Dis. Child.* 27: 204, 1924.
15. Cushing, H.: *Bull. Johns Hopkins Hosp.* 50: 137, 1932.
16. Deansley, R.: *Proc. Roy Soc., London*, s. B. 103: 523, 1928.
17. Fordyce, A. D., and Evans, W. H.: *Quart. J. Med.* 22: 557, 1929.
18. Frank, R. T.: *Proc. Soc. Exper. Biol. & Med.* 31: 1204, 1934.
19. Frazer, I.: *Brit. J. Surg.* 26: 521, 1940.
20. Gallagher, T. F.: Addenda in reprint.<sup>10</sup>
21. Gallais: *Rev. de gynéc. et de chir. abd.* 22: (No. 1), 1914.
22. Goormaghligh, N.: *Thèse de doct., Univ. de Gand. H., Liège*, 1922, Vaillant-Carmanne.
23. Green, R. R., and Ivy, A. C.: *Science* 86: 200, 1937.
24. Grollman, A.: *The Adrenals*, Baltimore, 1936, Williams & Wilkins Company.
25. Heath, F., Cahill, G. F., and Atchley, D. W.: *J. A. M. A.* 117: 1258, 1941.
26. Hoerr, N. L.: *Am. J. Anat.* 4: 135, 1931.
27. Holl, G.: *Deutsche Ztschr. f. Chir.* 226: 277, 1930.
28. Hyman, A., and Mencher, W. H.: *J. Urol.* 49: 755, 1943.
29. Kepler, E. J.: *Proc. Staff Meet., Mayo Clin.* 13: 353, 1938.
30. Lissner, H.: *Endocrinology* 20: 567, 1936.
31. O'Crowley, C. R., and Martland, H. S.: *J. Urol.* 50: 6, 1943.
32. Miller: *Am. J. Anat.* 40: 251, 1927.
33. Oppenheimer, B. S., and Silver, R. S.: *Tr. A. Am. Physicians* 52: 146, 1937.
34. Pardee, I.: *A. Research Nerve & Ment. Dis., Proc.* 17: 590, 1938.
35. Parkes-Weber, F., and Rowland, R. P.: *Guy's Hosp. Rep.* 79: 401, 1929.
36. Player, L. P., and Lissner, H.: *Tr. West. B. Assoc. A. U. A.* -2, 1933.
37. Reilly, W. A., Lissner, H., and Hinman, F.: *Endocrinology* 24: 91, 1939.
38. Rush, H. P., Bilderback, J. B., Slocum, D., and Rogers, A.: *Endocrinology* 21: 404, 1937.
39. Silver, S.: *Bull. New York Acad. Med.* 16: 368, 1940.
40. Simpson, S. L., and Joll, C. A.: *Endocrinology* 22: 595, 1938.
41. Simpson, S. L., de Fremery, P., and MacBeth, A.: *Endocrinology* 20: 363, 1936.
42. Slot, W. J. B.: *Acta med. Scandinav.* 89: 371, 1936.
43. Sudds, M. V. K.: *Endocrinology* 36: 895, 1930.
44. Walters, W., and Kepler, E. J.: *J. A. M. A.* 111: 1061, 1938.
45. Weil, P., and Browne, J. S. L.: *Science* 90: 445, 1939.
46. Weinberger, L. M., and Grant, F. C.: *Arch. Int. Med.* 67: 762, 1941.
47. Whitehead: *J. Anat.* 67: 387, 1933.
48. Wintersteiner, O.: *J. A. M. A.* 116: 2681, 1941.
49. Young, H. H.: *Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases*, Baltimore, 1937, Williams & Wilkins Company.
50. Zum Busch, J. P.: *Deutsche med. Wchnschr.* 53: 323, 1927.
51. Zwemer, R. L.: *Am. J. Path.* 12: 107, 1936.
52. Zwemer, R. L., Wotton, R. M., and Norkus, M. G.: *Anat. Rec.* 72: 249, 1938.

#### *Medullary Hormonal Tumors*

1. Beer, E., King, F. H., and Prinzmetal, M.: *Ann. Surg.* 106: 85, 1937.
2. Belt, A. E., and Powell, T. O.: *Surg., Gynec. & Obst.* 59: 9, 1934.
3. Binger, M. W., and Craig, W. M.: *Proc. Staff Meet., Mayo Clin.* 13: 17, 1938.
4. Biskind, G. R., Meyer, M. A., and Beadner, S.: *J. Clin. Endocrinol.* 2: 113, 1941.
5. Brunschurg, A., Humphreys, E., and Roome, N.: *SURGERY* 4: 361, 1938.

6. Brunshurg, A., and Humphreys, E.: J. A. M. A. 115: 355, 1940.
7. Burgess, A. M., Waterman, G. W., and Cutts, F. B.: Arch. Int. Med. 58: 433, 1936.
8. Coecler, F. A., Field, H., Jr., and Durent, T. M.: Arch. Surg. 28: 1136, 1934.
9. Edward, D. G. F.: J. Path. & Bact. 45: 391, 1937.
10. Evans, V. L.: J. Lab. & Clin. Med. 22: 1117, 1937.
11. Fein, H. J., and Carman, F. F.: Am. J. Cancer 29: 301, 1937.
12. Freeman, N. E., and Freedman, Miller: Am. J. Physiol. 131: 545, 1941.
13. Hamilton, J. E.: Kentucky M. J. 38: 572, 1940.
14. Heath, F., Cahill, G. F., and Atchley, D. W.: J. A. M. A. 117: 1258, 1941.
15. Holst, E. J.: Acta med. Scandinav. 94: 510, 1938.
16. Howard, J. E., and Barker, W. H.: Bull. Johns Hopkins Hosp. 61: 371, 1937.
17. Hyman, A., and Mencher, W. H.: J. Urol. 49: 755, 1943.
18. Kelly, H. M., Pipe, M. C., Wilder, R. H., and Walters, W.: Proc. Staff Meet., Mayo Clin. 11: 65, 1936.
19. Kremer, D. N.: Arch. Int. Med. 57: 999, 1936.
20. Labbé, M., and Tinel-Doumer, J.: Bull. et mém. Soc. méd. d'hôp. de Paris 46: 982, 1922.
21. Lazarus, J. A., and Eisenberg, A. A.: J. Urol. 27: 1, 1932.
22. McKenna, C. M., and Hines, L. E.: J. Urol. 34: 93, 1935.
23. MacKenzie, D. W., and MacEachern, D.: Tr. Am. A. Genito-Urin. Surgeons 31: 127, 1938.
24. MacKenzie, D. W., and MacEachern, D.: J. Urol. 40: 467, 1938.
25. Mayo, C. H.: J. A. M. A. 89: 1047, 1927.
26. Niezum, F. R., and Walton, J. W.: Am. Heart J. 16: 643, 1938.
27. Perkins, W. M., Swingle, W. W., Taylor, A. R., and Hays, H. W.: Am. J. Physiol. 123: 668, 1938.
28. Pineoffs, M. D.: Tr. A. Am. Physicians 44: 295, 1929.
29. Porter, M. R., and Porter, M. R., Jr.: Surg., Gynec. & Obst. 50: 160, 1930.
30. Rosenthal, D. B., and Willis, R. A.: J. Path. & Bact. 42: 599, 1936.
31. Van Epps, E. F., Hyndman, O. R., and Greene, J. A.: Arch. Int. Med. 65: 1123, 1940.
32. Vaquez, H., and Donzelot, E.: Presse méd. 34: 1329, 1926.
33. Vaquez, H., and Donzelot, E.: Presse méd. 37: 169, 1929.
34. Wells, A. H., and Boman, P. G.: J. A. M. A. 109: 1176, 1937.

# THE ENDOCRINE ACTIVITY OF THYROID TUMORS AND THE INFLUENCE OF THE THYROID HORMONE ON TUMORS IN GENERAL

JACOB LERMAN, M.D., BOSTON, MASS.

*(From the Thyroid Clinic of the Massachusetts General Hospital)*

THE relation of the thyroid to new growth has been under investigation for some time, but the results have been rather inconclusive. The problem may be divided into two main categories, namely, the effect of thyroid hormone on malignant tumors in general and the effect of thyroid neoplasms on hormone production.

## THYROID HORMONE VERSUS NEW GROWTHS

The chief function of the thyroid gland is the elaboration and storage of its hormone, thyroglobulin. This iodine-containing protein plays a vital role in the economy of the body. It regulates the rate of energy exchange, or metabolism. In addition, it has numerous other actions which are probably interrelated and dependent upon the main one, the calorogenic action. The thyroid affects growth, maturation and differentiation of tissues, the distribution of water, salts, and colloids in the body, the metabolism of carbohydrates, and the function of the neuromuscular and circulatory systems. It has some effects which are not clearly understood, such as the fluctuation in cholesterol metabolism, tolerance to certain drugs, absorption from the gastrointestinal tract, motility of the gastrointestinal tract, and the formation of blood. The function of the thyroid is still further complicated by its direct and indirect effect on the other endocrine glands, which, in turn, act upon the thyroid. The physiologic action of thyroid is best illustrated in the two clinical conditions of exophthalmic goiter and myxedema or cretinism. In the one, the manifestations of the disease, except for the eye signs, are due to excess secretion of thyroid; in the other they are due to undersecretion of thyroid.

In view of the profound effect that thyroid has on normal tissues, it has been assumed that this hormone would also affect the development and growth of abnormal tissues, such as neoplasms. A great deal of work has been done on this subject. Most of the results indicate that the state of thyroid function is not important in experimental tumors. Thyroxine has no influence on the incidence and growth of various types of transplantable mouse tumors (Sugiura and Benedict,<sup>1</sup> Salter, Nathanson, and Wilson<sup>2</sup>) or on rate of sarcoma production in

Received for publication, Sept. 28, 1943.

chickens (Okamura and Namiki<sup>3</sup>); thyroidectomy also is without effect on such tumors (Bischoff and Maxwell<sup>4</sup>). In the case of chemically induced tumors, the recent report of Smith, Wells, and D'Amour<sup>5</sup> indicates that neither thyroid administration nor thyroidectomy influences the incidence of tumor development. Such results agree with our clinical impression that the state of thyroid function has no influence on the incidence and growth of cancers in patients. In the past twelve years we have observed various kinds of malignancy six times in 150 patients with myxedema and seven times in 1,300 patients with hyperthyroidism. In addition, 2 patients were found to have teratomas of the ovary soon after they had been operated upon for Graves' disease. The higher incidence in myxedema than in hyperthyroidism is probably related to the higher average age of patients with myxedema.

In this connection we have observed an interesting phenomenon in one of the patients with myxedema who had an epithelioma of the nose. This lesion failed to heal in spite of repeated exposures to x-ray over a period of ten years. However, as soon as the patient became normal with thyroid administration the lesion healed completely and has remained so for eight years. What the explanation for this may be is not clear. It probably has to do with the increase in blood flow in the skin, the increase in metabolism of the epithelium, and the increased rate of desquamation of epithelial cells.

There are some reports which indicate that tumor growth is retarded in thyroidectomized animals (Nishida,<sup>6</sup> McJunkin, Templeton, and Kravec<sup>7</sup>). Similar results have been recorded for hibernation and for starvation. Either depression in metabolism, common to all three conditions, or some peculiar disturbance in nutrition, present in all three conditions, may account for these results. On the other hand, Gilroy<sup>8</sup> reports that thyroxine injected into mice retards the rate of tumor growth, an effect which may be neutralized by the administration of arginine. A possible explanation for these confusing results may lie in the unusual findings obtained by Meyer and McTiernan.<sup>9</sup> These investigators found that the oxygen consumption of malignant tumor tissue from thyroidectomized animals was slightly reduced, to 15 per cent below the average, but the oxygen consumption of tumor tissue from thyroxine-treated animals was also reduced and more so, an average of 25 per cent in three-fourths of the cases. Such results indicate that malignant growths are not under the usual physiologic control.

A point of interest is the effect of malignancy on the thyroid of the host. In experimental cancer there is reduction in height of epithelium, indicating diminished function, probably preceded by a short period of stimulation (Larionow,<sup>10</sup> Twort and Twort,<sup>11</sup> and Nishida<sup>6</sup>). In the advanced stages of the disease there is further depression of thyroid function. In patients with any type of cancer the basal metabolism

is frequently elevated (Jura<sup>12</sup>), probably as a result of the toxemia produced by the cancer rather than from stimulation of the thyroid gland. As cachexia develops the metabolism remains elevated or may actually increase, but the thyroid may become atrophied as a result of malnutrition.

#### ENDOCRINE ACTIVITY OF THYROID TUMORS

Pathologists dealing with malignant thyroid disease disagree about the proportion of thyroid carcinomas arising from previously existing benign adenomas. Some adenocarcinomas and the various types of sarcoma do not arise from previously existing tumors. The incidence of thyroid malignancy is about 1 to 4 per cent of nontoxic goiters.

The statistics of the older literature indicate that malignancy occurred largely in goitrous areas. However, the more recent figures from various clinics throughout this country are rather uniform. For example. Means<sup>13</sup> reports a 3.2 per cent incidence of thyroid cancer for the non-goitrous area around Boston, and Pemberton<sup>14</sup> reports a 2 to 5 per cent incidence for the goitrous region around Rochester. The figures from both areas are in relation to nontoxic nodular goiter.

The question whether malignant thyroid tumors and their metastases can function normally and, indeed, overfunctionate, has led to a good deal of speculation. The classical case of von Eiselsberg<sup>15</sup> has frequently been cited as evidence that metastases from thyroid cancers may function normally. His patient developed myxedema following removal of the thyroid for malignancy. Two years later, myxedema disappeared when the tumor, consisting of colloid-containing follicles, recurred in the manubrium. When the tumor was removed, myxedema returned. The occurrence of tetany along with myxedema and the disappearance of tetany as the tumor recurred is further evidence that the tumor in his case was producing thyroid hormone. On the other hand, there are reports which indicate that thyroid carcinoma or its metastases do not relieve coexisting myxedema (Gulliver<sup>16</sup>). The fact that myxedema seldom, if ever, occurs when the thyroid is diffusely malignant does not necessarily indicate that the malignant tissue is producing hormone. It is more likely that the uninvolved normal follicles are the sites of such activity.

More direct evidence of activity of thyroid tumors has been forthcoming. Although Marine and Johnson<sup>17</sup> found only minute amounts of iodine in 3 thyroid carcinomas and none in the metastases, and Eisen<sup>18</sup> found no iodine in 1, either in the original tumor or in its metastases, other observers have reported the presence of thyroid hormone in such tumors. Graham<sup>19</sup> found that the iodine content of adenomas and the effect on the metamorphosis of tadpoles varied with the degree of differentiation of adenomas. One fetal adenoma and one carcinoma, each of which contained only traces of iodine, still produced a definite accel-

eration of tadpole metamorphosis. Similarly, Milles,<sup>20</sup> using the Guderatsch test, and Engelstad,<sup>21</sup> using the Reid Hunt acetonitrile method, both showed that metastases from thyroid malignancy contained active hormone. Moreover, by means of the more recent refined methods of iodine analysis, it has been found that thyroid tumors do contain appreciable amounts of iodine. Hamilton and Soley,<sup>22</sup> using radioactive iodine as a tracer, determined that carcinomas of the thyroid take up 0.39 per cent radioactive iodine. The ratio of uptake was higher than normal, exceeded only by the hyperplastic glands due to iodine deficiency. Recently Keston, Ball, Frantz, and Palmer<sup>23</sup> reported that a femoral metastasis from a thyroid carcinoma took up 30 per cent of the radioactive iodine administered.

Another aspect of this problem centers about the question as to whether thyroid malignancy may be associated with hyperthyroidism. Means<sup>13</sup> states that he has not seen cancer of the thyroid in persons who have had toxic goiter. Similarly, Crile<sup>24</sup> did not find a single incidence of indisputable hyperthyroidism in 249 cases of thyroid malignancy, and came to the conclusion that the diagnosis of malignancy should be made with caution where evidence of hyperthyroidism is clear-cut. This would mean either that hyperplastic tissue cannot become malignant or that thyroid carcinoma cannot hyperfunctionate. Other investigators report different results. Clute<sup>25</sup> could find no case of cancer arising in a typical hyperplastic gland but did find 4 cases in which carcinoma developed in fetal adenoma associated with exophthalmic goiter. Coller<sup>26</sup> found only 1 case of thyroid carcinoma arising from a hyperplastic gland, and Pemberton,<sup>14</sup> studying the largest single group of thyroid tumors (774), found 10 patients with hyperthyroidism. In 4 the neoplasm was confined to adenoma in the gland; in 6 it developed within the gland. Goetsch<sup>27</sup> reported 7 instances in 52 cases of thyroid malignancy where the malignancy occurred in hyperplastic glands. He came to the conclusion that these tumors arose from pre-existing fetal rests or nodules and not from hyperplastic cells. The highest incidence of hyperthyroidism in thyroid malignancy has been reported by Welti and Huguenin<sup>28</sup> (8 in 88 cases of thyroid neoplasm), and by Friedell<sup>29</sup> (57 in 412 cases of adenocarcinoma). Part of the variation in reported results may be due to the fact that thyroid carcinoma is frequently associated with an elevated metabolism. But this also is true for nonthyroid carcinomas. The elevation of metabolism is not necessarily due to overfunction of the thyroid but rather to absorption of toxic products from the tumor and from structures destroyed by the tumor. Moreover, a false elevation in metabolism may be obtained, especially in patients with thyroid cancer, as a result of dyspnea and stridor which the thyroid mass may produce.

My own experience corresponds to that of Means and of Crile, with one exception. Recently I was invited by Dr. F. Reichenbach of the Westfield State Sanatorium to see a patient with toxic goiter and

widespread metastases from the thyroid. She was clinically hyperthyroid and had a basal metabolic rate of plus 87 which improved on iodine. A nodule had been present in her neck for many years but had caused no symptoms. Biopsies from the nodule in the neck and from one of the metastases revealed the histologic picture of normal thyroid tissue—an example of “benign metastasizing adenoma.”

I have also had the opportunity of studying the case history of another patient with hyperthyroidism and malignancy of the thyroid.\* This patient was suffering from hyperthyroidism in association with acromegaly, and required subtotal thyroidectomy in 1923. She remained symptom-free until 1932, although the picture of acromegaly progressed, when the goiter recurred as well as symptoms of hyperthyroidism. In 1933, the toxic symptoms became so severe as to necessitate a second thyroidectomy. At this time a nodular goiter which was grossly and microscopically malignant was found. Following heavy radiation the patient has been free from thyroid disease until the time of this communication.

In the first case it seems clear that a pre-existing adenoma was the cause of the thyroid malignancy. However, it was not possible to determine the source of hyperthyroidism. It was my opinion that the adenoma and metastases were not producing an excess of thyroid hormone, but that the remainder of the thyroid was hyperplastic and responsible for the thyrotoxicosis. In the second case it seems likely that the recurrence of hyperthyroidism did not result from malignant thyroid tissue but rather from regrowth of hyperplastic tissue due to pituitary stimulation. It is impossible to draw any conclusions as to the origin of the malignancy, whether from hyperplastic tissue or from a pre-existing adenoma.

A case report submitted to Dr. James H. Means by Dr. H. R. Peters of Baltimore suggests that aberrant thyroid tumor tissue, in this case in the ovary, is able to produce hyperthyroidism. Similar case reports have appeared in the literature.

Briefly, this patient, a woman, 41 years of age, suffered from hyperthyroidism of moderate severity for six months. Her basal metabolic rate level of plus 34 per cent did not change with iodine medication, and thyroidectomy was carried out. The tissue removed at operation showed hyperplasia and involution. In spite of an adequate operation she continued to suffer from symptoms of thyroid intoxication and the basal metabolic rate remained at plus 30. Five months after thyroidectomy a mass was discovered in the pelvis and removed surgically. Following the second operation the patient had a thyroid storm but recovered completely. Her metabolism dropped to minus 6 and she became free from thyrotoxic symptoms. Interestingly enough, the cyst removed turned out to be a teratoma, containing hyperplastic thyroid tissue which was partly involuted.

The most important aspect, clinically, of the problem of function of thyroid tumors revolves around the disease “toxic adenoma.” In

\*I am indebted to Dr. John C. Roe of Pittsfield for permission to mention this case.

any large group of patients with thyroid disease one finds a few showing mild hyperthyroidism, asymmetrical goiter, and little in the way of eye signs. At operation the surgeon may find, in a case of this type, a single nodule and normal-looking or slightly atrophic tissue surrounding it and also in the opposite lobe. Should the pathologist call this nodule an adenoma then one must hold with Plummer and call this a case of "toxic adenoma"—a truly hyperfunctionating neoplasm. However, many pathologists refuse to call this nodule anything but a discrete lump of hyperplastic tissue. In that event one cannot label this case as anything but a variant of ordinary thyrotoxicosis. It is my opinion that the argument for "toxic adenoma" is inadequate. I have seen several patients whose clinical picture was characteristic of Graves' disease—with moderate toxicity, eye signs present, and response to iodine. At operation only single nodules were found that appeared histologically like the diffuse hyperplasia of ordinary exophthalmic goiter. The remainder of the tissue was normal grossly and microscopically. Perhaps this problem cannot be settled until the pathologist is able to differentiate hyperplasia from neoplasia.

#### CONCLUSION

1. The state of thyroid function does not seem to influence greatly the development and growth of either experimental or human cancers. The slight retardation in tumor growth produced by thyroidectomy is probably due to associated nutritional disturbances. Thyroxine, under some conditions, may also depress tumor growth.

2. Malignant thyroid tumors and their metastases probably contain small amounts of thyroid hormone, the concentration depending on the degree of differentiation. The absence of myxedema in association with thyroid malignancy is not necessarily due to the production of hormone by malignant tissue but may be due to the function of uninvolved normal thyroid tissue.

3. The association of hyperthyroidism and thyroid cancer is rare. There is no evidence that thyroid malignancy can produce an excess of thyroid hormone or that hyperplastic tissue can become malignant. It is more likely that malignancy arises in a pre-existing adenoma imbedded in the hyperplastic gland.

4. Struma ovarii may produce clinical hyperthyroidism.

5. So-called "toxic adenoma" may not be a neoplasm at all, but rather the end result of a single focus of ordinary hyperplasia.

#### REFERENCES

1. Sugiura, K., and Benedict, S. R.: The Influence of Hormones on the Growth of Carcinoma, Sarcoma, and Melanoma in Animals, *Am. J. Cancer* 18: 583, 1933.
2. Salter, W. T., Nathanson, I. T., and Wilson, H.: Experimentally Induced Benignancy of Neoplasm, *Cancer Research* 1: 60, 1941.
3. Okamura, I., and Namiki, M.: Heterotransplantation des Tumors und Innersekretion, *Gann* 32: 279, 1938.



4. Bischoff, F., and Maxwell, L. C.: Hormones in Cancer. V. The Effect of Glandular Extirpation Upon the Growth of Transplantable Tumors, *J. Pharmacol. & Exper. Therap.* 46: 51, 1932.
5. Smith, D. L., Wells, J. A., and D'Amour, F. E.: The Relationship of the Endocrine System to Carcinogenesis, *Cancer Research* 2: 49, 1942.
6. Nishida, S.: Experimental Study of Effect of Thyroid Function on Growth of Malignant Tumor, *Jap. J. Obst. & Gynec.* 18: 195, 1935.
7. McJunkin, F. A., Templeton, R. D., and Kravce, F. G.: Resistance of Thyroparathyroidectomized Rats to Growth of a Spindle-Cell Sarcoma, *Proc. Soc. Exper. Biol. & Med.* 34: 801, 1936.
8. Gilroy, E.: Comparison of the Effects of Arginine and Thyroxine Upon Tumor Growth Rate in the Mouse, *Biochem. J.* 24: 1181, 1930.
9. Meyer, O. O., and McTiernan, C.: A Study of the Relationship of Internal Secretions to the Metabolism of Malignant Tumor Tissue, *Am. J. Cancer* 20: 96, 1934.
10. Larionow, L. T.: The Endocrine Glands in Experimental Cancer Induced by Benzpyrene, *Am. J. Cancer* 38: 492, 1940.
11. Twort, J. M., and Twort, C. C.: Studies on the Internal Organs of Mice Painted With Carcinogenic Agents, *Am. J. Cancer* 23: 52, 1935.
12. Jura, V.: Il metabolismo basale nei portatori di tumori maligni prima e dopo la loro asportazione, *Riv. di pat. sper.* 15: 35, 1935; abstracted in *Am. J. Cancer* 26: 625, 1936.
13. Means, J. H.: The Thyroid and Its Diseases, Philadelphia, 1937, J. B. Lippincott Co.
14. Pemberton, J. de J.: Malignant Lesions of the Thyroid Gland, *Tr. Am. A. Study Goiter*, p. 154, 1938.
15. von Eiselsberg, A.: *Arch. f. klin. Chir.* 48: 489, 1894.
16. Gulliver: Malignant Disease of the Thyroid Developing in a Case of Myxedema, *Tr. Path. Soc. London* 37: 511, 1886.
17. Marine, D., and Johnson, A. A.: Experimental Observations on the Effects of Administration of Iodin in Three Cases of Thyroid Carcinoma, *Arch. Int. Med.* 11: 288, 1913.
18. Eisen, D.: Malignant Tumors of the Thyroid: An Analysis of Seven Cases With a Study of the Structure and Function of the Metastases, *Am. J. M. Sc.* 170: 61, 1925.
19. Graham, A.: Study of the Physiological Activity of Adenomata of the Thyroid Gland, in Relation to Their Iodine Content, as Evidenced by Feeding Experiments Upon Tadpoles, *J. Exper. Med.* 24: 345, 1916.
20. Milles, G.: A Principle Accelerating Growth and Maturation Demonstrated in Metastases of a Tumor of the Thyroid Gland, *Arch. Path.* 17: 631, 1934.
21. Engelstad, R. B.: The Thyroxin Production in Metastases From Carcinoma of the Thyroid, *Am. J. Cancer* 26: 738, 1936.
22. Hamilton, J. G., and Soley, M. H.: Studies in Iodine Metabolism by Use of a New Radioactive Isotope of Iodine, *Am. J. Physiol.* 127: 557, 1939.
23. Keston, A. S., Ball, R. P., Frantz, V. K., and Palmer, W. W.: Storage of Radioactive Iodine in a Metastasis From Thyroid Carcinoma, *Science* 95: 362, 1942.
24. Crile, G., Jr.: Hyperthyroidism Associated With Malignant Tumors of the Thyroid Gland, *Surg., Gynec. & Obst.* 62: 995, 1936.
25. Clute, H. M.: Exophthalmic Goiter and Cancer of the Thyroid Gland, *S. Clin. North America* 13: 759, 1933.
26. Coller, F. A.: Adenoma and Cancer of the Thyroid, *J. A. M. A.* 92: 457, 1929.
27. Goetsch, E.: Incipient Carcinoma Occurring in Exophthalmic Goiter and Originating in Adenoma, *Tr. Am. A. Study Goiter* p. 191, 1940.
28. Welti, H., and Huguenin, R.: Malignant Tumors of the Thyroid Gland, *Tr. Am. A. Study Goiter*, p. 141, 1938.
29. Friedell, M. T.: Hyperthyroidism and Adenocarcinoma of the Thyroid Gland, *Arch. Surg.* 43: 386, 1941.

## THE ENDOCRINE ASPECT OF ENLARGEMENTS OF THE PARATHYROID GLANDS

OLIVER COPE, M.D., BOSTON, MASS.

*(From the Department of Surgery of the Harvard Medical School and the Surgical Services of the Massachusetts General Hospital)*

DISEASE associated with tumor or hyperplasia of the parathyroid glands has been considered rare. This is because the glands defy detection and because the misconception is held that bone disease is a requisite of parathyroid disease. Parathyroid disease frequently exists; it is merely not diagnosed and not proved.

Although the parathyroid glands were described as anatomic structures as long ago as 1880, by Sandstrom,<sup>1</sup> pathologists were unable to contribute much to the description of parathyroid diseases; the parathyroid glands are small, of a color hard to differentiate, in position various, and they are, therefore, found only after painstaking search even at an autopsy. Parathyroid adenomas were found post mortem (Askanazy, 1904)<sup>2</sup> in certain cases of a bone disease with tumors, cysts, and generalized decalcification (osteitis fibrosa cystica generalisata or von Recklinghausen's disease, 1891).<sup>3</sup> But it was wrongly construed that the parathyroid enlargement was secondary to the bone abnormalities. It was not until 1925 that Mandl,<sup>4</sup> a surgeon in Vienna, tested the concept that the parathyroid tumor was the cause of the bone changes. After excising a parathyroid tumor from a patient with von Recklinghausen's disease, calcium was again deposited in the bones and hyperparathyroidism was established as an entity.

It was correctly assumed after 1925 that the clinically important primary disease of the parathyroid glands was the endocrine one associated with hyperfunction, that is, excessive production of hormone. Reports of some eighty-five cases of generalized osteitis fibrosa cystica associated with a parathyroid tumor had appeared in the literature by 1932. In contrast, first, only two cases of primary or idiopathic hypoparathyroidism<sup>5</sup> had been reported. Second, a few cases of a malignant tumor of the neck, supposedly in a parathyroid gland, were described; histologically difficult to prove, certainly some of the cases were doubtful. And finally, no case of a nonmalignant tumor of a parathyroid gland not associated with hyperfunction had been reported.

As a result of Mandl's discovery and various experimental pathologic observations, the idea became firmly established that the parathyroid hormone acts directly on bone and that any functional disturbance of the parathyroid glands must of necessity result in bone changes. Al-

The classic bone disease form of hyperparathyroidism is readily diagnosed; the roentgenogram is characteristic. Metabolic studies are unnecessary but, if made, the abnormalities are readily spotted even by inexperienced technicians. The patients with the renal complications and little or no bone disease, however, have generally a milder form of the disease and it is only with painstaking effort and persistent study that the disease is diagnosed.\* In some of the cases of this series the diagnosis was not established until the offending gland had been excised and a change in metabolism demonstrated.

The first case studied in this country was at the Massachusetts General Hospital. Each successive case was investigated so thoroughly from the physiologic point of view that it became possible to forecast variations in the disease. It was in this manner that the primary hyperparathyroidism without the bone complications was established.

*Physiology of the Parathyroid Hormone.*—The end results of the action of the parathyroid hormone are well known. How the hormone effects these results remains a matter of conjecture.

There are four salient features of the action of this hormone. It exerts a control over the distribution of both calcium and inorganic phosphate ions in the blood stream and probably in all of the body fluids. Whether the hormone acts primarily on the phosphate or the calcium ion is not clear; the majority opinion favors the calcium ion. With increased activity, the level of the calcium ion in the blood serum is raised and that of the phosphate ion depressed. There is an increased outflow of both calcium and phosphate through the kidney while there is sometimes a slightly diminished fecal calcium excretion. In hypoparathyroidism the reverse of these effects is true.

The primary site of action of the hormone is not clear. It has been suggested that it is in either the kidney or the bone. The best evidence against an action in the bone, at least as far as decalcifying the bone is concerned, is the clinical finding that hyperparathyroidism exists without demonstrable changes in the bones, either microscopically or by roentgen ray, and that the phosphatase level of the blood serum is more often normal than elevated. It is possible that the hormone affects cells and that its influence on ion distribution in the body fluids is secondary.

The reason certain cases of hyperparathyroidism develop decalcification is due to the hormone's action in increasing excretion of calcium. If the intestinal tract is absorbing sufficient calcium, that is, if there is sufficient calcium in the diet, the excess excreted comes from that absorbed and the patient does not develop bone disease. If the diet is low in calcium, the excretion is at the expense of the bones, which are the storehouse for calcium. When the reserve calcium in the trabeculae of the bone is gone, the calcium is taken from the cortex.

\*The number of cases diagnosed at this hospital is due to the enthusiasm and vigilance of Dr. Fuller Albright.

It is not understood why certain of those patients whose bone reserves are called upon to feed the disease process develop the complicated, distorted picture of osteitis fibrosa cystica instead of simple decalcification or osteoporosis. Possibly a greater rapidity of removal of calcium with overactivity of foreign body giant cells has something to do with the giant tumor formation so characteristic of this specialized form. It is also possible that conditions affecting the regeneration of the bone matrix, such as the lack of sex hormone after the menopause, swing the balance in favor of osteoporosis.

Since kidney stones may be a complication of hyperparathyroidism, it is imperative for physicians to understand the disordered physiology of the disease in order to differentiate stones due to hyperparathyroidism from those due to other causes. As has already been suggested, the elevation of the calcium ion causes decrease in muscular tone. (This is, of course, the reverse of the tetany occurring with hypoparathyroidism and decreased calcium ion in the body fluids.) This decrease in tone is associated with a lack of vigor and lassitude and often not appreciated by the patient until the offending gland has been excised and well-being returns. There may be mild, bizarre gastrointestinal complaints, perhaps with constipation. But usually the patient feels perfectly well and may be surprised at attention to anything but the presenting renal stone. Fatigue exists with greater elevations of the blood calcium. The polyuria and polydipsia are unpredictable symptoms; the physiologic basis presumably is the same controlling that in diabetes mellitus except in those patients who have developed impairment in renal function.

The commonest renal symptoms of the disease come from calculi. The increased output of calcium by the kidney results in supersaturation of the urine. The calcium precipitates out usually as a phosphate salt since the phosphate ion is always in excess; this is particularly true if the urine is alkaline when the phosphates are most insoluble. On the other hand, if oxalate is present, calcium oxalate may be formed. This is more likely when the urine is acid and the oxalate the more insoluble. Stones, therefore, may contain one or other salt, or mixtures, but always calcium. The precipitation may occur anywhere in the urinary tract. If it occurs in kidney substance along the tubules, gradual impairment in renal function occurs. If it takes place in the lumen of the tubules, calcium phosphate casts result. The finding of such granular casts in the urine is presumptive evidence of hyperparathyroidism.<sup>7</sup>

If the precipitate starts in a calyx or pelvis of the kidney, stone formation results. The symptoms are those of any stone in this position; the stones frequently become dislodged and pass into the ureter with serious consequences. Primary bladder and prostatic stones have been observed in our cases. Presumably these were due to the presence of urea-splitting organisms. The ammonia formed by the bacteria alkalizes the urine at this level and causes precipitation of calcium phosphate.

# CASE REPORT ILLUSTRATING DIFFERENTIAL DIAGNOSIS BETWEEN PRIMARY AND SECONDARY HYPERPARATHYROIDISM

CASE 68.\*—A man, aged 68 years, first entered the hospital April 27, 1940, to receive roentgen-ray therapy to a basal-cell carcinoma of the scalp. The scalp lesions had been noted eleven years previously and had been treated elsewhere by excisions with grafting, and radium. He had additional complaints; for the previous one and one-half years, weakness, especially of the legs, had been progressive, and for the previous few months the patient had been bedridden. Neurologic study showed no reason for the weakness.

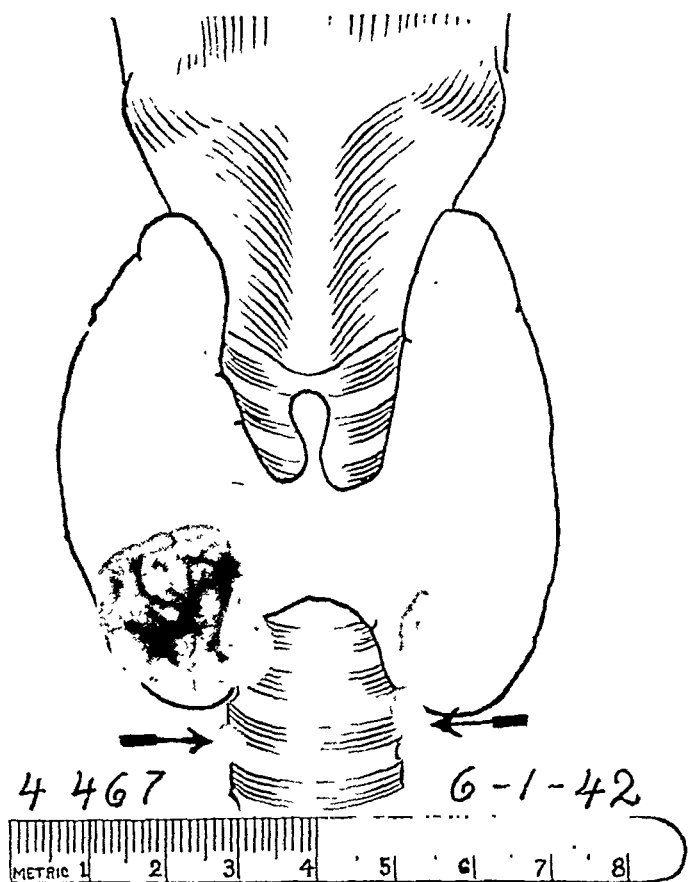


Fig. 1.—The parathyroid adenoma and the three uninvolved parathyroid glands found post mortem in Case 68. The specimens are photographed on a diagram in their relative positions to the thyroid. Arrows point to the two lower glands.

*Roentgenograms.*—Lateral roentgenogram of the skull showed diffuse small rarified areas; that of the chest was negative. The spine and pelvis were diffusely decalcified with a single cystlike area of destruction in the second lumbar vertebra and another in the crest of the ilium. A diagnosis of multiple myeloma was made from the roentgenograms.

Chemical studies of blood and urine failed to reveal the Bence-Jones protein or the elevated serum protein expected in multiple myeloma. The blood serum calcium

\*Each case of hyperparathyroidism of the Massachusetts General Hospital series is given a number when the diagnosis is proved. The same case numbers are used in all publications on this subject from this hospital.

level was 11.2 mg. per 100 c.c., serum phosphorus 5.3 mg., and phosphatase 17.1 units (Bodansky). There was a moderate amount of calcium in the urine, a specific gravity not higher than 1.016, and intermittent albumin. Phenolsulfonephthalein excretion was only 10 to 12 per cent in two hours. A tentative diagnosis of primary hyperparathyroidism with secondary impairment of renal function was made.

Further roentgen-ray study showed decalcification of the bones of the extremities with an irregular moth-eaten appearance of some of the finger phalanges and metacarpals. A diagnosis of hyperparathyroidism was made from the roentgenograms. Additional chemical studies showed a blood serum calcium level varying between 10.0 and 11.3 mg., phosphorus 4.7 to 5.6 mg., phosphatase 19 to 22.5 units. There was a persistently high blood chloride level from 107 to 115 meq./l and low  $\text{CO}_2$  of 16 to 24 meq./l. The serum protein was 6.4 Gm., nonprotein nitrogen 29 mg., and uric acid 6.6 mg.

A biopsy of the skull was decided upon but on the way to the operating room the patient vomited a large amount of blood and went into collapse; no bone was removed. The patient vomited blood on several other occasions. Gastrointestinal roentgen-ray studies were negative. Free acid was present in the gastric juice in normal amounts.

The medical service decided that the patient probably had primary renal disease with secondary hyperparathyroidism. The surgical service, on the other hand, judged the hyperparathyroidism to be primary, basing the decision on the slightly elevated serum calcium level (11.3 mg., the highest). Had the parathyroid overactivity been initiated by the phosphate retention, the calcium level should still have been below normal (see under Secondary Hyperparathyroidism). Operation was not advisable, however, since the renal disease had progressed to such an extent that some degree of hyperparathyroidism was thought necessary to maintain the calcium level. The elevated phosphate level would depress the calcium once any tumor was removed and the other parathyroid glands would undergo secondary hyperplasia. One form of hyperparathyroidism would be exchanged for another.

The patient was discharged and followed in the outpatient department. Sodium citrate was prescribed for the acidosis. The patient accomplished a shift in chloride and  $\text{CO}_2$  back to normal at intervals. Clinically the patient was stronger but decalcification, as judged by roentgenograms, progressed. The blood levels of calcium, phosphorus, and phosphatase continued in the same range.

Finally, May 15, 1942, the patient re-entered the hospital with a diagnosis of pyelonephritis from which he succumbed, June 6, 1942.

At post-mortem examination, a typical, brown, encapsulated adenoma of the right upper parathyroid was found, measuring 22 by 6 mm. and weighing 2.4 Gm. (Fig. 1). The three other glands were normal in size, shape, and color. The calvarium was thin and flexible, bending like a hoop; giant cell tumors were grossly recognizable. The ilium contained a large cyst; elsewhere it and the spine were osteoporotic. The ribs were extensively decalcified and were cut with ease.

The kidney parenchyma had been severely damaged. Nowhere did the cortex measure more than 3 mm. in thickness. The corticomedullary margin could scarcely be made out and the pyramids were small and distorted. The calices of the right kidney were dilated. In the cardia of the stomach were two small leiomyomas. Microscopic sections of the lungs showed pathologic calcification.

This patient illustrates the difficulty of making the differential diagnosis between primary and secondary hyperparathyroidism in the presence of impaired renal function. He proved to have the primary form of the disease, since he had an adenoma and three uninvolved glands.

Unfortunately, making the diagnosis in this case was only of academic significance.

*Benign Tumor Without Hyperfunction.*—No case of a benign tumor of a parathyroid gland not associated with an excess in output of hormone has been reported. It is possible that they have been overlooked, have been thought to be thyroid, or have not been reported. That they occur is suggested by a patient operated upon in this hospital<sup>8</sup> and by the occasional finding at post mortem of small adenomas.<sup>12</sup> In neither of these instances, however, could pre-existing hyperparathyroidism be excluded, for the presence of a parathyroid tumor had not been suspected before either operation or death and the appropriate chemical studies had not been made.

M. G. H.<sup>7</sup> (H. No. 221018).—A woman, aged 70 years, was admitted to the hospital in October, 1939, with a diagnosis of intestinal obstruction. She had had "bilious" attacks since childhood. Five months before entry she had first noticed a lump in the left lower abdomen which had persisted. Recently she had noticed cramps radiating down the left leg associated with nausea and vomiting. There was also constipation. Abdominal examination was negative. Gastrointestinal studies were entirely negative. A nodule in one side of the thyroid was found. Roentgenogram of the chest showed old healed apical tuberculosis but no metastases. Roentgenograms of pelvis and spine were also negative for metastases.

At operation the "thyroid" lump was found to be a parathyroid adenoma measuring 6 by 3 by 3 cm. It was excised and consisted almost entirely of pale oxyphil cells; there was no evidence of malignancy.

On the fourth postoperative day a blood serum phosphorus determination was 3.8 mg. per 100 c.c. Before operation the blood nonprotein nitrogen was 2.5 mg. per 100 c.c., chloride 96 meq./L., and serum protein 7.2 Gm. No other blood studies were made. She was discharged home on the seventh postoperative day. Seven days later she suddenly died of heart failure according to her family physician.

A parathyroid tumor was not suspected preoperatively and the chemical studies necessary to exclude hyperfunction were, therefore, not made. It is probable, however, since there was no clinical tetany after removal of the tumor, that hyperfunction did not exist. This belief is strengthened by Castleman's opinion that the presence of pale oxyphil cells in large numbers in an adenoma indicate nonhyperfunction.

The tumors found at post-mortem examination by Castleman and Mallory<sup>12</sup> were minute, far too small to be appreciated clinically. Since all parathyroid glands are not examined at every postmortem examination at this hospital, we have no accurate idea of the incidence of such benign tumors.

*Malignant Tumors.*—Malignant tumors arising in parathyroid tissue have been reported but they are rare. Some twenty-two cases are reported in the literature; a good many of these are open to question since the descriptive details are meager. It is possible that the tumors

<sup>8</sup>I am indebted to Dr. Marshall K. Bartlett for permission to report this case.

in some arose from other tissue, and that others were not malignant.\* There are two, recent well-reported cases in which reference to the others may be found. The tumor reported by Meyer, Rosi, and Ragins<sup>12</sup> from the Cook County Hospital was accompanied by undeniable hyperfunction. The malignant tumor of the other case, reported from California by Hall and Chaffin,<sup>16</sup> presumably did not secrete any excess of hormone.

#### PATHOLOGY

Enlargements of the parathyroid glands are due either to hyperplasia or neoplasia. Disordered function is associated always with the first and usually with the second. A functional or endocrine classification of the pathology of parathyroid enlargements is given in Table III.

TABLE III  
FUNCTIONAL CLASSIFICATION OF PARATHYROID ENLARGEMENTS

<i>Hyperplasia</i>	
	Primary hyperplasia with hyperfunction*
	Secondary hyperplasia with hyperfunction
	Chronic nephritis
	Vitamin D deficiency—rickets, osteomalacia
	Pregnancy
<i>Neoplasia—Benign</i>	
	Adenoma without hyperfunction
	Adenoma with hyperfunction
<i>Neoplasia—Malignant</i>	
	Carcinoma without hyperfunction
	Carcinoma with hyperfunction

\*Albright believes that hypertrophy is the proper designation for this pathologic entity.<sup>17</sup>

No attempt is made in this communication to give full anatomic consideration. Excellent details regarding parathyroid cell types and full discussion of the pathologic theory of neoplasia are given in the review by Castleman and Mallory.<sup>12</sup> The pathology of the secondary hyperplasia of the parathyroid glands in nephritis is fully described in the articles by Pappenheimer and Wilens<sup>9</sup> and Castleman and Mallory.<sup>10</sup>

*Primary Hyperplasia With Hyperfunction.*—Seven of the seventy-eight cases of primary hyperparathyroidism seen at the Massachusetts General Hospital have been due to a primary hyperplasia involving all four parathyroid glands. This disease type is presumably comparable to the hyperplasia encountered in thyrotoxicosis. In thyroid disease it is, however, the common type producing thyrotoxicosis, true toxic neoplasia of the thyroid being relatively rare. No clinical difference in the hyperparathyroidism produced by this pathologic type has been determined

\*It may be difficult to decide whether the tumor is malignant. Dr. Broders of the Mayo Clinic and Dr. Castleman and Dr. Mallory of this hospital, for example, are not in agreement about the malignancy in the case reported by Snell.<sup>13</sup> After reviewing slides of the tumor, which Dr. Broders very kindly sent on, Dr. Castleman and Dr. Mallory feel it is typical of what they classify as benign neoplasia. They also have placed the case reported by Wellbrock<sup>14</sup> in the same category.



from that associated with neoplasia of the parathyroids. All of the characteristics of the hyperparathyroidism due to adenoma with bone and renal complications have been encountered in the seven cases due to hyperplasia. Search for other hormonal differences, such as increased pituitary hormones in the urine, have so far proved fruitless. Since this disease type is diffuse and involves all of the parathyroid tissue present, presumably the original stimulus is different from that causing neoplasia or localized disease.

The primary hyperplastic gland is grossly distinguishable from the adenoma. The surface contours are more irregular, often with deep sulci and irregular peninsulas. The color is also a deeper brown.

On microscopic section the cells are all of one type, the Wasserhelle or clear cell. There is no fat in the glands and the parathyroid cells are usually concentrically arranged with nuclei near the periphery. These cells are large and distended and measurements by Albright show that individual cells are as much as sixty times larger than those of the normal gland. Mitotic figures are rare and Albright feels that these enlargements represent hypertrophy, enlargement of the individual cells, rather than hyperplasia, increase in number of cells.<sup>17</sup> Castleman<sup>18</sup> says Albright's concept may be right but the necessary meticulous and time-consuming microscopic measurements and counts have not been done.

The gross appearance of these primary hyperplastic glands is sufficiently characteristic to be recognized at operation. It is wise, however, to check the gross observation with frozen section. A pathologist, trained in this work, can readily recognize the concentric, vacuolated cell.

*Secondary Hyperplasia with Hyperfunction.*—The type of hyperplasia which occurs in response to increased physiologic demand is grossly and microscopically different from the primary type. In the first place the enlargement is not as great. In vitamin D deficiency (rickets in the child and osteomalacia in the adult), and in pregnancy, the hyperplasia of the epithelial elements is mild; grossly the enlargement is not more than two to four times the normal. There is no distortion of shape or pseudopod formation. Since the enlargement is not great enough to eliminate the fat cells by compression, the color remains nearly the light brown of the normal gland.\* Following long-standing nephritis, this secondary hyperplasia may continue until the individual gland weighs thirtyfold the normal.

The microscope shows the hyperplastic cells to be entirely chief cells; no water-clear cells are seen.

A mild degree of secondary hyperplasia may be difficult to recognize grossly (or even microscopically on frozen section) at operation. Long training at the post-mortem table is necessary.

\*The color of the normal parathyroid gland depends upon the proportion of epithelial to fat cells contained within the gland capsule. The parathyroid epithelial cells are brown. The fewer the fat cells, therefore, the browner the gland.

*Adenoma Without Hyperfunction.*—The adenoma without hyperfunction differs in no way grossly from that forming an excessive secretion. The one large and few small adenomas of this type which have been encountered in this hospital have shown nonvacuolated epithelial cells, usually of the pale oxyphil type; no fat was present between the epithelial cords. The large adenoma removed by Bartlett at operation weighed 23 Gm. The small ones recovered at the post-mortem table have been scarcely large enough to be recognized grossly.

*Adenoma With Hyperfunction.*—Benign neoplasia or adenoma is the common pathologic type encountered in primary hyperparathyroidism. Seventy-one of the seventy-eight proved cases at the Massachusetts General Hospital were of this type. Usually the adenoma is single, involving only one of the four parathyroid glands. Five of the seventy-one patients, however, have proved to have two adenomas, one in each of two glands. The adenomas vary considerably in size; several of them have been very small, two of them were not more than 2 mm. in diameter and occupied only part of the space within the gland capsule, the remainder of the tissue being normal. In such cases the adenoma may be hard to recognize, for the presenting surface of the gland may be normal tissue.

It is not until the gland is turned over or cut into that the darker brown of the adenoma without fat cells is recognized. With increase in size, the normal tissue is apparently destroyed by compression within the capsule. With their browner color, the larger adenomas are readily recognized. The surface is generally smooth and pseudopods are rare. The color varies from light, to dark, to greenish brown. Sometimes there are small cysts within them. The largest tumor in this series weighed 53 Gm. (Larger tumors have been reported.<sup>13</sup>) The size of the adenoma is roughly proportional to the elevation of the blood calcium above normal.

Microscopically, adenomas have been found to contain all of the various cell types. Some are composed of one type alone and others of mixtures. Fat cells in the stroma are rare.

*Carcinoma.*—No case of carcinoma of the parathyroid gland has been recognized at this hospital. That such malignant tumors do occur has already been alluded to and reference should be made to the reports of Meyer, Rosi, and Ragins<sup>15</sup> and Hall and Chaffin.<sup>16</sup> It is probable that such malignant tumors are rare since it is difficult to imagine that a cancer would be overlooked even in a routine post-mortem examination where no effort is made to identify the parathyroid glands.

It is possible that the relative incidence of malignant to nonmalignant neoplasia is the same in both the parathyroid and thyroid glands. Carcinoma of the thyroid is not infrequent but abnormalities of the thyroid gland are probably far more numerous than those of the parathyroid. It has been denied that carcinoma of the thyroid can be associated

with hypersecretion. Certainly in the case of the parathyroid, carcinomatous tissue can secrete an excess of hormone.

*Atrophy.*—Primary atrophy with hypoparathyroidism is a clinical curiosity, but secondary atrophy of the uninvolved glands in the presence of a hyperfunctioning adenoma is common and of direct clinical and surgical importance. If an atrophic gland is uncovered at operation, the atrophy points to the presence of a hyperfunctioning adenoma in another gland. This secondary atrophy, or atrophy of disuse, can be recognized grossly by the surgeon.

The atrophic glands are not only smaller than the expected normal but the color is yellower since the atrophy affects the epithelial and not the fat cells. In the presence of a long-standing, active adenoma, the atrophy may proceed to such a degree that grossly the uninvolved atrophic gland resembles fat and is recognized only by its capsule and characteristically arranged blood supply. A piece of one such gland was removed for biopsy and the microscopic sections showed complete absence, or atrophy, of epithelial elements. Milder degrees of atrophy may be harder to recognize both grossly and microscopically because of the variation in fat content of the normal gland.

*Bone and Kidney.*—Bone and kidney are not endocrine tissue but are the structures most commonly affected in the complications of hyperparathyroidism. The reader is referred to the article by Jaffe on osteitis fibrosa cystica generalisata<sup>19</sup> for an account of this specialized type of bone pathology. It should be recalled, however, that diffuse osteoporosis or decalcification also follows overactivity of the parathyroid gland. No adequate description of this pathologic type has appeared; a report by Albright and co-workers<sup>20</sup> contains certain thoughts on this subject. The pathology of the kidney, secondary to hyperparathyroidism, is briefly described by Albright and his associates.<sup>21</sup>

Pathologic calcification occurs elsewhere in the body in severe cases of hyperparathyroidism. Calcification of arteries is not infrequently seen by roentgenogram. In the Massachusetts General Hospital series, calcification of the gastric mucosa was found post mortem in Case 6, and of the lung in Case 68 (see case report in this communication). Such calcification has been demonstrated in experimental animals with parathyroid poisoning.

#### TREATMENT

It is not the purpose of this article to deal in detail with treatment. For a complete discussion of this aspect of the parathyroid problem, reference should be made to the other articles from this hospital.

Medical therapy in the form of a high calcium diet has been suggested for hyperparathyroidism. It is true that the bones can be recalcified<sup>21</sup> in the presence of the active parathyroid disease but kidney damage is accelerated. With the increased intake of calcium from the intestinal

tract the bones are spared but the load of the kidney is multiplied. Rapid calcification of renal tubules and stone formation may result in progressive impairment of renal function. Stones can be removed but the impairment due to renal calcification has, in our experience, proved irreversible.

Roentgen-ray treatment in hyperparathyroidism has been ineffectual; this is discussed in detail elsewhere.<sup>22</sup> The use of irradiation in the treatment of carcinoma of the parathyroids has not been reported.

The treatment of parathyroid enlargements, tumor or hyperplasia, is surgical. If a tumor is not accompanied by disordered function, it should be excised with capsule intact. If the tumor is malignant, radical excision including the area of lymphatic drainage is indicated. The use of postoperative irradiation should be considered.

If hyperparathyroidism is present there are special considerations which should guide the surgeon in his attack. These have been fully described elsewhere.<sup>23</sup> The operation may have to be divided into two stages (10 per cent of cases). Subtotal excision of primary hyperplastic glands is always indicated, and of an adenoma, in the presence of extensive bone disease, sometimes.

#### SUMMARY

Enlargements of the parathyroid glands are not uncommon. Those associated with hyperfunction are clinically the most important. The endocrine considerations of the hyperplasia and tumors causing primary and secondary hyperparathyroidism have been discussed. A case of hyperparathyroidism with severe renal damage is described to illustrate the difficulty in differentiating between primary and secondary hyperparathyroidism, and also to emphasize the renal complications of this disease. A functional classification of the pathology of parathyroid enlargements is given. The clinical types of hyperparathyroidism encountered in the seventy-eight cases of the Massachusetts General Hospital series are given in table form. The treatment of parathyroid enlargements is surgical.

#### REFERENCES

1. Sandstrom, I.: Om en ny Körtel hos menniskan och åtskilliga däggdjur, *Upsala läkaref. förh.* 15: 441, 1880.
2. Askanazy, M.: Ueber Ostitis deformans ohne osteoides Gewebe, *Arb. a. d. Geb. d. path. Anat.* 4: 398, 1904.
3. Von Recklinghausen, F.: Die fibröse oder deformirende Ostitis, die Osteomalacie und die osteoplastische Carcinose, in ihren gegenseitigen Beziehungen, *Festschrift R. Virchow zu seinem, 71 Geburtstag*, Berlin, 1891, G. Reiner.
4. Mandl, F.: Therapeutischer Versuch bei Ostitis fibrosa generalisata mittels Exstirpation eines Epithelkörperchentumors, *Wien. klin. Wchnschr.* 38: 1343, 1925.
5. Aub, J. C., Albright, F., Bauer, W., and Rossmeisl, E.: Studies of Calcium and Phosphorus Metabolism. VI. In Hypoparathyroidism and Chronic Steatorrhea With Tetany With Special Consideration of the Therapeutic Effect of Thyroid, *J. Clin. Investigation* 11: 211, 1932.

6. Wilder, R. M., and Howell, L. P.: Etiology and Diagnosis in Hyperparathyroidism. A Review of One Hundred and Thirty-Five Proved Cases, *J. A. M. A.* 106: 427, 1936.
7. Albright, F., and Bloomberg, E.: Hyperparathyroidism and Renal Disease. With a Note as to the Formation of Calcium Casts in This Disease, *Tr. Am. A. Genito-Urin. Surgeons* 27: 195, 1934.
8. Barney, J. D., and Sulkowitch, H. W.: Progress in the Management of Urinary Calculi, *J. Urol.* 37: 746, 1937.
9. Pappenheimer, A. M., and Wilens, S. L.: Enlargement of the Parathyroid Glands in Renal Disease, *Am. J. Path.* 11: 73, 1935.
10. Castleman, B., and Mallory, T. B.: Parathyroid Hyperplasia in Chronic Renal Insufficiency, *Am. J. Path.* 13: 553, 1937.
11. Albright, F.: Renal Osteitis Fibrosa Cystica. Report of a Case With Discussion of Metabolic Aspects, *Tr. A. Am. Physicians* 51: 199, 1936.
12. Castleman, B., and Mallory, T. B.: The Pathology of the Parathyroid Gland in Hyperparathyroidism. A Study of 25 Cases, *Am. J. Path.* 11: 1, 1935.
13. Snell, A. M., and Mayo, C. W.: Report of a Case of Hyperparathyroidism, *Proc. Staff Meet., Mayo Clin.* 11: 633, 1936.
14. Wellbrock, W. L. A.: Malignant Adenoma of the Parathyroid Glands, *Endocrinology* 13: 285, 1929.
15. Meyer, K. A., Rosi, P. A., and Ragins, A. B.: Carcinoma of the Parathyroid Gland, *SURGERY* 6: 190, 1939.
16. Hall, E. M., and Chaffin, L.: Malignant Tumors of the Parathyroid Glands, *West. J. Surg.* 42: 578, 1934; Final Report of a Case of Malignant Adenoma of the Parathyroid Glands, *West. J. Surg.* 48: 685, 1940.
17. Albright, F., Sulkowitch, H. W., and Bloomberg, E.: Hyperparathyroidism Due to Idiopathic Hypertrophy (Hyperplasia ?) of Parathyroid Tissue, *Arch. Int. Med.* 62: 199, 1938.
18. Castleman, B.: Personal Communication.
19. Jaffe, H. L.: Hyperparathyroidism (Recklinghausen's Disease of Bone), *Arch. Path.* 16: 63-112, 236-258, 1933.
20. Albright, F., Burnett, C. H., Cope, O., and Parson, W.: Acute Atrophy of Bone (Osteoporosis) Simulating Hyperparathyroidism, *J. Clin. Endocrinol.* 1: 711, 1941.
21. Albright, F., Baird, P. C., Cope, O., and Parson, W.: Studies on the Physiology of the Parathyroid Glands. I. The Effect of Hyperparathyroidism, *Am. J. M. Sc.* 187: 49, 1934.
22. Cope, O.: Hyperparathyroidism: 67 Cases in Ten Years, *J. Missouri M. A.* 39: 273, 1942.
23. Cope, O.: Surgery of Hyperparathyroidism: The Occurrence of Parathyroids in the Anterior Mediastinum and the Division of the Operation into Two Stages, *Ann. Surg.* 114: 706, 1941.

## HYPERINSULINISM IN RELATION TO PANCREATIC TUMORS

ALLEN O. WHIPPLE, M.D., NEW YORK, N. Y.

*(From the Department of Surgery, Columbia University)*

THE endocrine function of the pancreas in carbohydrate metabolism is now well established but the story of the development of our knowledge of the internal secretion of islet cells is a long one. In 1788, Cawley<sup>1</sup> reported the autopsy findings of pancreatic calculi in a patient dying of diabetes mellitus. This was perhaps the first time that the pancreas was suspected of having an etiologic relationship to diabetes. Claude Bernard<sup>2</sup> discussed glycosuria and hyperglycemia, in 1856. In 1869, Paul Langerhans,<sup>3</sup> while still a medical student in Berlin, published his remarkable histologic studies of the pancreas in his inaugural dissertation. Using the transillumination method in living tissue, as did Lister<sup>4</sup> in his study of inflammation and recently revived by Knisely<sup>5</sup> in the study of the spleen, Langerhans described the several types of cells and tissues in the pancreas, and by his original method of dye injections showed the acinar gland tissue to be separate from islet tissue.

These collections of cells, which he termed "unser zellen," were given scant notice. In 1884, Arnozan and Vaillard<sup>6</sup> ligated the ducts of the pancreas and noted an atrophy of the acinar tissue and the persistence of islet cells, but did not attribute any significance to these cells in the fact that the animal did not develop a diabetes.

In 1890, von Mering and Minkowski<sup>7</sup> proved experimentally that a fatal diabetes can be produced in animals by total pancreatectomy. Two years later Minkowski<sup>8</sup> carried out an even more conclusive experiment. He successfully grafted pancreatic tissue subcutaneously. In the same animal the remaining pancreas was excised later without the development of glycosuria; but on removal of the graft the animal died of a rapidly developing diabetes. An endocrine function was postulated but the exact tissue involved was not proved.

In 1882, Kühne and Lea<sup>9</sup> described the capillary network surrounding the collections of islet cells, but did not contribute to the morphology of the cells themselves. In 1893 appeared the first report of a very real student of the endocrine function of the pancreas. In this report Laguesse<sup>10</sup> discussed the islet cells and generously called attention to their discoverer and named them "les îlots de Langerhans." He de-

The Trimble Lecture, read at a meeting of the Medical and Chirurgical Faculty of the State of Maryland, Baltimore, April 25, 1944.

Received for publication, May 12, 1944.

scribed the histology of the cells, including the granules, and the capillary network, and suggested the possibility of an endocrine function of these cells.

In 1895, Schäfer<sup>11</sup> called attention to the evidence in favor of an internal secretion of the pancreas as shown by fatal diabetes with total pancreatectomy while a total external fistula resulted in no diabetes. In 1900, Ssobolew,<sup>12</sup> as a result of duct ligation experiments with persistent islands, predicted that the study of the chemistry of these isolated islands would place organotherapy in diabetes on a rational basis. He even advised the use of newborn animals (calves) in which the islands are well developed in comparison with the acinar tissue, and made the following prediction: "We are justified in the hope that in the near future the question will be decided whether or not this method of approach will succeed in relieving the ills of the diabetic patient."

During the next twenty years a number of investigators were very near the crucial demonstration of this internal secretion, but failed because the extract of the islet tissue was not used in sufficient amount in a totally pancreatectomized animal with diabetes, or because of impurities in the extract. It remained for Banting and Best<sup>13</sup> of Toronto to demonstrate to an expectant world, by positive and conclusive experimental physiology, that islet tissue has an internal secretion, since named insulin, and that it can be used successfully in the control of diabetes. Their epoch-making announcement was made in 1922.<sup>13, 14</sup>

During this period of 1900 to 1922 a number of contributions were made in the histologic field. Opie,<sup>15</sup> in 1901, described hyaline changes in the islet cells of diabetics. In 1906 and 1908, Lane,<sup>16</sup> by special technique, demonstrated two types of granule-containing islet cells and called them the *alpha* and *beta* cells. Bensley,<sup>17</sup> in 1912, described a vital staining technique for counting the islands in the guinea pig and demonstrated that islet cells are derived from duct epithelium.

Homans<sup>18</sup> studied experimental diabetes and, in 1915, showed changes in the *beta* cells of the islands. After the discovery of insulin Copp and Barclay,<sup>19</sup> repeating Homan's experiments, demonstrated that administration of insulin restored the exhausted *beta* cells.

In 1930, O'Leary,<sup>20</sup> using transillumination in the pancreas of the mouse fed with glucose, was able to see vacuoles form in the islet cells. These vacuoles migrated to the periphery of the cells next to the capillaries into which they apparently disappeared by diffusion.

#### PATHOLOGY OF ISLET TISSUE

The study of degenerative changes in the pancreas in diabetes began with Hanseman's<sup>21</sup> report, in 1894, on fibrosis and atrophy of the pancreas in diabetic patients. Ssobolew's<sup>12</sup> observations and Opie's,<sup>15</sup> which were made independently, have been mentioned. Homans,<sup>18</sup> in 1915,

described changes in experimental diabetes in the dog's pancreas confined to the *beta* cells of the islands.

It was not until the significance of the islands as insulin-producing cells was understood, and not before the syndrome of insulin shock was appreciated, that the islet-cell tumors or hyperplasias received any attention by the pathologists. In 1902, Nicholls<sup>22</sup> described the first of these tumors, but gave no clinical history. Ssobolew,<sup>23</sup> in 1904, was the first to report a hypertrophied island in the autopsy of a diabetic. Herxheimer,<sup>24</sup> in 1905, and MacCallum,<sup>25</sup> in 1907, described similar findings. In 1920, Dubreuil and Anderodias<sup>26</sup> made a most interesting autopsy report on the hypertrophied islands of a newborn infant of a diabetic mother.

Even as late as 1926, four years after the discovery of insulin, only sixteen islet-cell tumors had been described. In that year Warren<sup>27</sup> reviewed these and four of his own cases, but no physiologic significance was attached to these growths. In the same year Gray and Feemster<sup>28</sup> described the hypertrophied islands of an infant born of a mother with diabetes. The child died of convulsions shortly after birth. Shortly after the phenomenon of overdosage of insulin began to be observed by those who were using insulin to treat patients with diabetes, Seale Harris of Birmingham, Ala., noted very much the same syndrome in patients showing a hypoglycemia and the idea occurred to him that overactive islet tissue, either as hyperplastic or neoplastic cells, might explain the clinical picture which he had observed in these patients. Harris discussed this possibility with Banting who agreed with him in his hypothesis, and published his report<sup>29</sup> entitled "Hyperinsulinism and Dysinsulinism," in 1924. Three years later a physician suffering with the syndrome of severe insulin shock went to Rochester, Minn., and was studied by Wilder and his associates.<sup>30</sup> The patient was operated upon by W. J. Mayo, who found a tumor of the pancreas with metastases to the liver. The biopsy showed an islet-cell tumor. Several weeks later autopsy revealed the same tumor and a biologic assay of the liver metastases showed large amounts of insulin in the tumor tissue.

In 1929, Graham of Toronto removed for the first time a benign adenoma of islet tissue from a woman who had been studied by Howland and his associates.<sup>31</sup> The patient was immediately relieved of her symptoms and has remained well to date. This initiated a new and the latest phase of endocrine surgery, a type of surgery requiring the skill in diagnosis and operative technique previously demonstrated in the removal of tumors or hyperplasias of the thyroid, pituitary, adrenal, and parathyroid glands.

Since 1929, well over 149 islet-cell tumors have been found in patients showing hypoglycemia, some by surgeons, the rest by pathologists. Of these tumors, 106 were pronounced benign adenomas, 28 questionably malignant; in 15 cases the tumors were unquestionably malignant because of metastases to the liver or adjacent lymph nodes.



At this point it should be stated that hypoglycemia may occur without any demonstrable lesion in the pancreas, and that tumors, having all the morphologic characteristics of islet-cell growths, may be found by the surgeon or pathologist, without any of the symptoms or laboratory findings of the hypoglycemic state. Furthermore, the size of the tumor in cases of hypoglycemia does not necessarily determine the degree of insulin shock. But the carcinomas of islet tissue with metastases always show severe symptoms and very low fasting blood sugars.

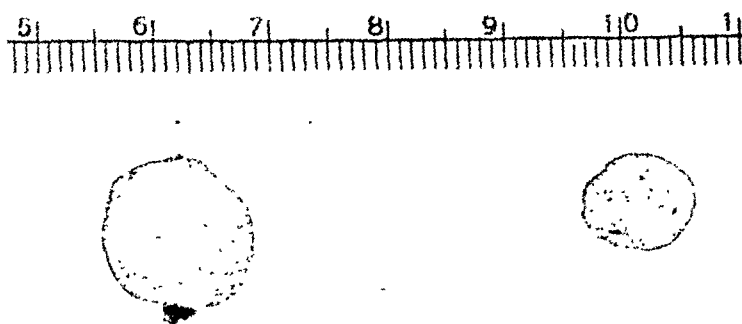


Fig. 1.—Two islet-cell tumors from same patient removed at one operation.

In general these islet-cell tumors are small, averaging 1 to 2 cm. in diameter. The largest tumor, one reported by Brunschwig,<sup>32</sup> measured 15 by 13 by 10 cm. but did not show more severe symptoms of hypoglycemia than many other tumors of 2 cm. diameter. The largest tumor removed by the writer (3 cm. in diameter) was palpable before operation and was considered to be a tumor of the pylorus because of x-ray studies and showed no symptoms of hypoglycemia. These tumors are more frequently found in the tail or body of the pancreas where islet tissue is more abundant. But enough of these tumors are found in the head of the pancreas, in twelve cases in our series, to demand a thorough search of the head by mobilizing the duodenum so that the head can be palpated between thumb and fingers. Furthermore, more than one tumor has been found in hypoglycemic cases. For this reason a thorough search of the entire organ after the finding of one tumor should be made.

In the gross the benign tumors are encapsulated, as are many of the questionably malignant ones. These tumors are usually of a reddish to lilac color, as contrasted with the yellowish or ivory color of the surrounding pancreas, because of their rich capillary network. Many of the tumors show various types of degeneration, as hyaline and fibrous, and some are markedly calcified. In consistency they are definitely firmer than the surrounding pancreatic tissue and feel like encapsulated marbles to the palpating fingers. For this reason they have

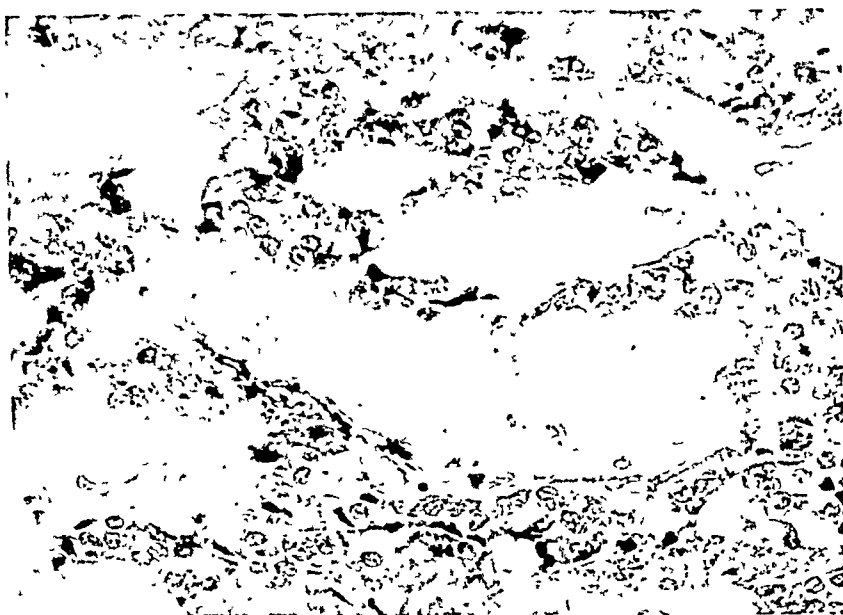


Fig. 2.—Hyaline degeneration of islet-cell tumor.

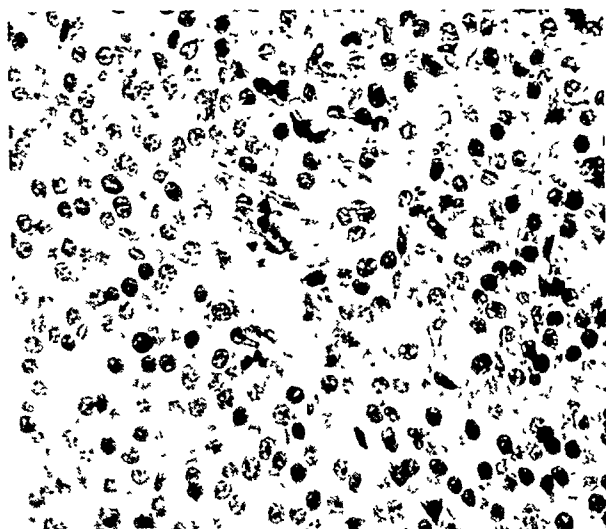


Fig. 3.—Adenomatous arrangement of islet-cell tumor.

to be palpated between thumb and fingers of the surgeon's hand if they are deeply embedded in pancreatic tissue and not visible on the anterior surface of the organ.

On microscopic examination these tumors, benign, questionably malignant, or malignant, all show cells typical of islet cells, but they

differ markedly in their arrangement and differentiation. Some are typically adenomatous, resembling hundreds of agglomerated islands; others are less well differentiated with the cells arranged in ribbons or in scattered collections of islet cells with varying amounts of degenerated fibrous tissue; still others, in the questionably malignant group, show less differentiation with some invasion of the capsule and the presence of islet cells in the capillary vessels; and lastly the definitely malignant tumors show lymph node, liver, and other metastases.

In all of these tumors the demonstration of the *alpha* and *beta* cells requires careful differential stains in freshly removed tumors and even with these stains it is difficult or impossible to demonstrate these cells.



FIG. 4.—Glandular arrange.

The most difficult group of these to interpret and to prognosticate are the early growths. Brantz,<sup>10</sup> of our surgical department, has studied the histology of these tumors and has published her report in her last two paragraphs:

It seems improbable that all of the tumors of carcinoma were really such, as the percentage of carcinoma is so high, 21 to 70, and the follow-

It would be gratifying to feel that surgery had eliminated malignant disease in all these cases. But, of these suspected tumors, are there some in which blood vessel invasion, demonstrated, means that metastases, not demonstrable, were present at the time of removal of the primary growth, and will these eventually develop symptoms of hyperinsulinism?

If one wishes to consider the so-called "adenoma malignum" type of carcinoma of the thyroid as possibly analogous to these well-differentiated islet cell tumors with blood vessel invasion, then it might be that, like the thyroid tumors of this type, distant metastases might be late and slow. But the metastasizing tumors of the thyroid do not give evidence of their presence by hyperthyroidism, and it is conceivable that even in small metastatic foci of islet cell tumors hypoglycemia might occur early. Thus far no reported case has illustrated this, but it seems a good possibility. How long one should wait to feel secure about such functional metastases, and whether one can predicate that symptoms should appear early, is pure speculation. It will be of the utmost importance to follow all of these patients with these rare tumors for many years, and in the event of recurrence, or metastases after apparently successful removal, to publish such findings so that clinician and pathologist will have some basis for prognosis.

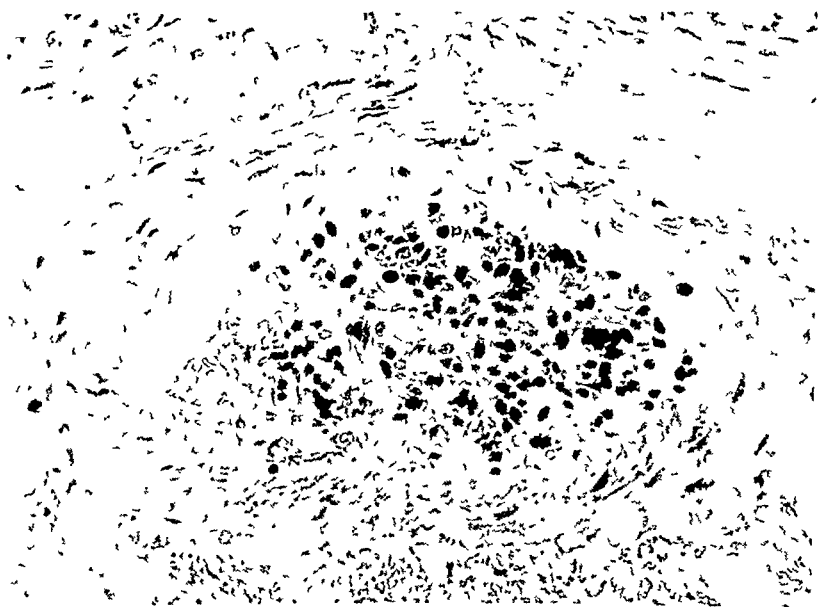


Fig 5—Islet cells in blood vessels of a questionably malignant islet-cell tumor

We now have 8 of these cases, with death in 1 and follow-up studies in 7 of them, the postoperative interval being 72, 48, 24, 14, 12, 8, and 4 months. None of these patients has as yet shown evidences of recurrent hypoglycemic symptoms, which one would expect with even small recurrent growths of this type of endocrine tumors.

More recently Duff<sup>14</sup> has published a comprehensive review of this subject and records 12 cases of islet-cell carcinoma with tumor metastases. The reader interested in a more detailed discussion of the gross

and microscopic findings in islet-cell tumors in general is referred to the reports of Whipple and Frantz,<sup>35</sup> Frantz,<sup>33</sup> O'Leary and Womack,<sup>36</sup> Laidlaw,<sup>37</sup> and the most recent article by Duff.<sup>34</sup>

#### THE ORIGIN OF ISLET-CELL TUMORS

The genesis of these tumors has been studied by Bensley<sup>38</sup> and Grauer<sup>39</sup> on the basis of the embryology and regenerative process in the pancreas. They have demonstrated that the epithelial cells of the islands in the embryo differentiate from the epithelial cells of the small ducts of the pancreas. This ability of duct epithelium to differentiate either into islet tissue or normal ducts is seen in the adult pancreas that is regenerating after the release of experimental duct ligation. This may explain the occasional finding of an islet-cell tumor without evidences of hyperinsulinism. That is, such a tumor may not have taken on the physiology of islet tissue, although having the morphology of islet tissue.

#### FACTORS IN BLOOD SUGAR MAINTENANCE

A very confusing factor in many individuals with the syndrome of hypoglycemia is the question of whether or not hyperinsulinism is the cause of the hypoglycemia. The latter can be measured by blood sugar determinations, but the former is not as yet measurable. But hypoglycemia is not always the result of an overproduction of insulin. The maintenance of the normal blood sugar level is the result of an interplay of several organs, especially the pancreas, the liver, the hypophysis, the adrenals, and the thyroid. Carbohydrate ingestion in the normal individual, or the withholding of it, does not play as important a part in the maintenance of normal blood sugar level as one would suppose. It is certain lesions in the previously mentioned organs that cause a hypoglycemia. Regarding the liver, Mann<sup>40</sup> in his experiments with complete and partial removal of that organ has proved the essential role of the liver in this respect. Bodansky,<sup>41</sup> Underhill,<sup>42</sup> and Sprague<sup>43</sup> have demonstrated the effects of liver damage in the maintenance of normal blood sugar.

Of equal significance is the work that has been done in showing the role of the anterior lobe of the hypophysis in the maintenance of the blood sugar, especially that of the Argentinian Houssay.<sup>44</sup> Hypophysectomy causes a marked fall in the fasting blood sugar, as well as a marked sensitivity to insulin injection. In a totally depancreatized animal with diabetes, removal of the anterior lobe of the hypophysis will prolong the life of the animal and even glycosuria may disappear. Young<sup>45</sup> has been able to produce experimentally a permanent diabetes in dogs by the injection of an extract of anterior pituitary lobe, but he considers this a somewhat different type of diabetes from the pancreatic variety.

That there may be an intermediary action by the adrenal cortex on the anterior lobe of the hypophysis in its influence on carbohydrate metabolism is strongly suggested by the studies of Long and Lukens.<sup>46</sup> Womack<sup>47</sup> suggests that the action of the sympathetic system and the thyroid gland in the maintenance of blood sugar levels is similar to that of the adrenal medulla in mobilizing sugar from the liver.

It is obvious that the hypoglycemic state requires a careful search for the cause of the low blood sugar and that hyperinsulinism must not be assumed to be the cause until lesions or disturbances in the liver, the pituitary, the adrenals, and the thyroid have been ruled out. In liver lesions causing hypoglycemia the patients are gravely ill and show other obvious signs of liver damage. Similarly the cases due to adrenal disease are not easily confused with hyperinsulinism, for the patients are usually seriously ill with Addison's disease or show signs of adrenal tumor. The low blood sugar levels associated with hypophyseal lesions are likely to cause more confusion, but they are usually associated with tumors causing headache and with visual field disturbances, and show x-ray evidence of widening or destruction of the sella turcica. In cases of hypoglycemia with hyperthyroidism the basal metabolism rate is apt to be lower than in other cases of Graves' disease and these patients may develop a thyroid storm after the removal of an islet-cell tumor. For this reason a basal metabolic determination should be done in all cases of suspected islet-cell tumor, and if the rate is above 15 the patient should be given a course of iodine therapy as in preparation for a thyroid operation.

Finally, cases of epilepsy may mimic the syndrome of hyperinsulinism, because of the occurrence of "fits" or "spells." Electroencephalograms have proved of the greatest help in differentiating the epileptiform attacks from those seen in hyperinsulinism.

#### THE SYNDROME OF HYPERINSULINISM DUE TO ISLET-CELL TUMOR

Hypoglycemia due to hyperinsulinism may be the result of overproduction of insulin by overactive normal islands, by hyperplastic islands, or by tumors of islet cells, or it may be due to an overdose of insulin. The syndrome of hyperinsulinism is as varied in its manifestations as is insulin shock, for they are the same.

The "attacks," "fits," or "spells," as they are spoken of by the patient or his family, are extremely variable in their manifestations in different individuals but as a rule maintain the same general pattern, varying in severity, in the same individual. Wilder<sup>48</sup> has wisely grouped the nervous manifestations of these attacks under three main headings: Those relating to disturbances of the vegetative nervous system, appearing as nausea, sweating, pallor, flushing, chilliness, syncope; those related to the central nervous system, manifested by restlessness, tonic or clonic muscle spasms, opisthotonos, convulsions; and lastly those

manifestations less readily localizable under the heading of psychic disturbances such as apprehensiveness, confusion, disorientation, mania, unconsciousness, and coma.

Less frequently associated with these "attacks" are digestive disturbances and abdominal pain, at times so severe as to be mistaken for lesions requiring surgery. Harris<sup>49</sup> and Bickel<sup>50</sup> have called attention to these gastrointestinal manifestations:

1. The "attacks" come on characteristically in the early morning during the fasting period before breakfast or after severe mental or physical effort when the sugar reserves are low

2. During the "attacks" or "spells" or after a fast of twelve to twenty-four hours the blood sugar levels are always below 50 mg. per cent; and finally

3. The victims of these spells are brought back to a normal state, that is, recover from whatever their "pattern" may be, on the administration of sugar by mouth or by vein.

This essential triad which we first emphasized in our report published in 1938<sup>51</sup> has been corroborated in practically all of the subsequent cases and the triad has come to be considered as a *sine qua non* for the diagnosis of hyperinsulinism due to an islet-cell tumor. Because we have adhered to this rigid criterion we have found a tumor in 27 of the 32 patients upon whom we have operated for the hypoglycemic state. This is a much higher percentage of positive findings than that reported from any other series of operations. In only 1 of the 5 patients we explored without the finding of a tumor was the triad typical. In the other 4 we had made reservations regarding the diagnosis and were doubtful of the presence of a tumor.

#### THE DIFFERENTIAL DIAGNOSIS OF ISLET-CELL TUMOR WITH HYPOGLYCEMIA REQUIRING SURGERY

In many cases of hypoglycemia surgical therapy is either not required because the symptoms are controlled by conservative measures or is contraindicated because the hypoglycemia is due to causes other than islet-cell tumor. These have been discussed under the last heading.

In the study of these cases in which tumor was suspected the establishment of the triad depends upon certain laboratory studies, the most important being at least three fasting blood sugar determinations, for it will be found that these levels will vary. If after twelve hours the blood sugar is not below 50, a longer fast should be given, under supervision, to make sure the patient is not taking any food. These fasting blood sugar determinations are by far the most important of the laboratory studies. The glucose tolerance test is only misleading in its information. It is more of a liver function test and should be reserved for the period during which the electroencephalogram pattern is being studied.

## THE SURGICAL THERAPY FOR ISLET-CELL TUMOR

For the patient exhibiting the typical triad and in whom hepatic, pituitary, adrenal, thyroid disease and epilepsy have been ruled out, surgery is definitely indicated. The three chief reasons for not continuing conservative therapy are:

1. Continuous administering of sugar and carbohydrate to control, but not cure, recurring insulin shock in these cases usually results in great obesity and when finally surgery is advised as a last resort, the patients have become a bad risk and a very difficult technical problem for the surgeon. Twenty-four of the 32 patients reported from this clinic were obese at the time of operation and several of them excessively so, one weighing 235, one 240, and one 278 pounds (Fig. 6).



Fig. 6.—A problem in surgery as a result of obesity.

2. Prolonged hypoglycemia has a tendency to cause mental deterioration, probably due to malnutrition of the cortical cells. Two of our patients with tumors had been in mental institutions, and one of them has had to be readmitted to a mental hospital several times, having returned there at the time of this communication, although the hypoglycemia has been cured. Three others are mildly peculiar.



3. The uncertainty of when a benign islet cell tumor may show malignant changes is a definite reason for not postponing surgery in a patient with a definite diagnosis of islet-cell tumor.

The confidence of the well-trained surgeon to explore and to resect the pancreas has increased amazingly in the past ten years, for in this time astonishing advances have been made in the surgery of pancreatic tumors. Adequate incisions, better anesthesia, and the use of fine silk, with the more delicate handling of tissues and the reduced trauma and better hemostasis that "silk technique" connotes, as well as present-day methods of preventing and combating shock, are the chief factors in broadening the field of pancreatic surgery.

As a result of experience in islet-tissue tumors, resections of the body and tail, and pancreatoduodenectomy for carcinoma of the ampullary and periampullary areas, we have adopted the following measures and technique for the surgery of islet tumors:

1. It is essential to give the patient an ample supply of glucose before the operation. We give 1,000 c.c. of 5 per cent glucose in normal saline solution intravenously one hour before operation and leave the needle in the vein for a transfusion, if necessary, at the end of the procedure.

2. Both continuous spinal anesthesia and ether anesthesia have been used, depending upon the individual indications. Excessive obesity is a contraindication for spinal anesthesia.

3. We are convinced that an adequate incision is essential and the long curved transverse incision just above the umbilicus through both recti, followed by the division of the gastrocolic omentum, provides a free inspection of the entire pancreas.

4. The islet tumors are most frequently found in the tail or body, and should be looked for there first. If a tumor is not seen on the anterior surface, the peritoneal attachment along the inferior border should be divided and, by blunt dissection and elevation, the posterior surface of body and tail should be inspected. If none is seen, the gland should be carefully palpated. The islet tumors feel like discrete nodules firmer than the surrounding pancreatic tissue even when imbedded in the body and head of the organ, and are unmistakable.

5. If no tumor is seen or felt in the body or tail, the duodenum should be mobilized to the midline by incision of the peritoneum along the curve of the duodenum. This gives access to the posterior surface and permits the essential and free palpation of the head of the pancreas. In 6 of our patients the tumors were situated in the posterior aspect of the ampulla of Vater and the most careful dissection was required to insure injury of the papilla in removal of the tumor.

If carcinoma is found, the same careful search must be made in the head of the pancreas, for one tumor may be present. In 3 of our 27 cases more

7. In removing the adenoma bleeding, as a rule, is very easily controlled, and the nodule shells out easily. Drainage is not necessary unless there is pancreatic duct leakage.

8. If no tumor is found after the very complete exploration described, the decision as to resection will have to be made. In the cases where no tumor was found and the body and tail, that is, to the left of the superior mesenteric vessels, have been removed, the results have been much better than the removal of a small portion such as the tail. In order to carry out this radical resection, it is advisable to remove the spleen as well, in order to control hemorrhage by ligating the splenic vessels supplying the body and tail of the pancreas. A wide division of the gastrocolic and gastrosplenic omenta will facilitate this splenectomy through the lesser sac, and make it possible to remove the spleen, tail, and body of the pancreas en masse. This maneuver also makes it possible to see and identify the inferior mesenteric vein and the superior mesenteric vessels.

9. The bed of the pancreas should be drained after ligating the pancreatic duct, by rubber dam tubes or cigarette drain.

10. The use of fine silk for all smaller vessels and a heavier grade for the larger vessels will prevent the digestion of ligatures which occurs when catgut is used in pancreatic tissue. Fine interrupted silk sutures for the repair of the abdominal wall have given us primary union in all our cases of adenoma and the same invariable satisfaction in wound healing that was noted by Kocher, Halsted, and other meticulous surgeons familiar with silk technique.

In reviewing the results of surgical therapy for islet-cell tumors in this series, it is obvious that excision of adenomas and so-called questionably malignant tumors gives brilliant and lasting cures of the hypoglycemic state. On the other hand, in the majority of the patients in whom an islet-cell tumor was not discovered and a partial pancreatectomy was done results were not good, either because a tumor was overlooked in the head of the organ or because an insufficient amount of the pancreas was removed. This is demonstrated by the fact that an overlooked tumor was found at the second operation in eight patients, four of whom we had explored the first time and the other four in other clinics. The fact that seven of the overlooked tumors were in the head of the pancreas emphasizes the importance of an adequate exposure by a transverse incision with mobilization of the duodenum so that all parts of the head of the organ can be carefully palpated. The recurrence or persistence of hypoglycemia below the 50 mg. per cent level after a partial pancreatectomy is almost certain evidence of an overlooked islet-cell tumor.

The prognosis in carcinoma of islet tissue, that is with metastases, is invariably bad. Even the use of alloxan, as suggested by the work of Dunn,<sup>52</sup> and as tried by Brunschwig and associates<sup>53</sup> in a recently reported case, does not offer any result.

Four patients, although relieved of their hypoglycemia, have continued in a more or less unstable mental state and one of them has had to be committed to a mental hospital. All of these patients had had a severe hypoglycemia for from two to six years. This is a definite reason for advising surgery as soon as the diagnosis of islet-cell tumor with hypoglycemia is established.

TABLE I  
SUMMARY OF STATISTICS

	SINGLE	MULTIPLE	TOTAL	% MULTIPLE
Tumors removed at operation and considered benign	65	11	76	
Tumors found at autopsy and considered benign	26	4	30	
Total benign tumors	91	15	106	14.2
Tumors removed at operation and suspected malignant	22	4	26	
Tumors found at autopsy and suspected malignant	2	0	2	
Total tumors suspected malignant	24	4	28	14.3
Total cases of tumor without proved malignancy	115	19	134	14.2
Carcinoma with metastases, proved malignancy	12	3	15	20.0
Total cases of true neoplasm	127	22	149	14.8
Hypertrophy and hyperplasia without neoplasm			11	

TABLE II  
SUMMARY OF ISLET-CELL TUMORS  
(Presbyterian Hospital Series, to March 15, 1944)

Number of patients explored	32
Tumor found in	27
Number of tumors removed	31
No tumor found	5
Tumor found at second operation	8
Postoperative deaths	3
adenoma	1
questionably malignant	1
von Gierke's disease	1

TABLE III  
PATHOLOGY OF TUMORS (TO MARCH 15, 1944)

Adenomas	16
Questionably malignant	8
Carcinoma	1
Adenomatosis	2
Total	27

Multiple tumors found in 4 patients.

Islet-cell tumors without hypoglycemia in two patients.

TABLE IV  
LOCATION OF TUMORS

In head of pancreas	12
In body of pancreas	8
In tail of pancreas	10
In liver	1

TABLE V  
SUMMARY OF OPERATIVE PROCEDURES

Excision of tumor	16
Partial pancreatectomy with tumor	5
Partial pancreatectomy without tumor	5
Removal of overlooked tumor	8
Simple exploratory	4

TABLE VI  
RESULTS AFTER OPERATION (TO MARCH 15, 1944)

	CURED OF HYPOGLYCEMIA	IMPROVED	UNIMPROVED	POSTOPERA- TIVE DEATHS
Adenoma	15			1
Questionably ma- lignant	72, 48, 24, 14, 12, 8, 4 mo. after oper- ation			1
Carcinoma			Died 4 mo. later	
Adenomatosis	16, 5 mo. after op- eration			
von Gierke's disease				1
No tumor found		2	3	

TABLE VII  
LENGTH OF THE FOLLOW-UP INTERVAL (TO MARCH 15, 1944)

	ADENOMAS	QUESTIONABLY MALIGNANT	ADENOMATO- SIS	CARCINOMA
9 yr.	4			
8 yr.	1			
6 yr.	1	1		
5 yr.	2			
4 yr.	2	1		
2 yr.	1	1		
1 yr.	2	2	1	
Less than 1 yr.	2	2	1	

## REFERENCES

1. Cawley, T.: A Singular Case of Diabetes, Consisting Entirely in the Quality of the Urine, *London Med. J.* 9: 286, 1788.
2. Bernard, C.: *Memoire sur le pancreas et sur le rôle du suc pancréatique dans les phénomènes digestifs*, *Compt. rend. Acad. d. sc. (Supp.)* 1: 379-563, 1856.
3. Laugerhans, P.: *Beiträge zur mikroskopischen Anatomie der Bauchspeicheldrüse*, Berlin, 1869, Lange, 32 pp.
4. Lister, J.: On the Early States of Inflammation, *Philosoph. Transactions*, 148: 645-702, 1858.

5. Knisely, M. H.: Microscopic Observations on Circulatory Systems of Living Transilluminated Mammalian Spleens and Parturient Uteri, *Proc. Soc. Exper. Biol. & Med.* 32: 212-214, 1934.
6. Arnozan, X., and Vaillard, L.: Contribution a l'étude du pancreas du lapin; lésions provoquées par la ligature du canal de Wirsung, *Arch. de Physiolog. Norm. et Path.* 3: 287, 1884.
7. von Mering, J., and Minkowski, O.: Diabetes Mellitus nach Pankreas extirpation, *Arch. f. exper. Path. u. Pharmakol.* 26: 371, 1890.
8. Minkowski, O.: Weitere Mittheilungen über den Diabetes Mellitus nach Extirpation des Pankreas, *Klin. Wehnschr.* 29: 90, 1892.
9. Kuhne, W., and Lea, A. S. L.: Beobachtungen ueber die Absonderung des Pankreas, *Untersuch. a. d. physiol. Institut. d. Heidelberg* 2: 488, 1882.
10. Laguesse, E.: Sur la formation des îlots de Langerhans dans les pancréas, *Compt. rend. Soc. de biol.* 45: 819, 1893.
11. Schäfer, L. A.: Internal Secretions, *Lancet* 2: 321, 1895.
12. Ssobolew, L. W.: Ueber die Structur der Bauchspeicheldrüse unter gewissen pathologischen Bedingungen, *Zentralbl. f. allg. Path. u. Path. Anat.* 11: 202, 1900.
13. Banting, F. G., and Best, C. H.: Internal Secretion of the Pancreas, *J. Lab. & Clin. Med.* 7: 251, 1922.
14. Banting, F. G., Best, C. H., and others: Pancreatic Extracts in the Treatment of Diabetes Mellitus, *Canad. M. A. J.* 12: 141, 1922.
15. Opie, E. L.: The Relation of Diabetes Mellitus to Lesions of the Pancreas, *J. Exper. Med.* 5: 527, 1901.
16. Lane, M. A.: On the So-called Transitional Cells of Lewaschew in the Islets of Langerhans, *Am. J. Anat.* 5: 16, 1906.  
Idem: The Cytological Characters of the Areas of Langerhans, *Am. J. Anat.* 7: 409, 1908.
17. Bensley, R. R.: Studies on the Pancreas of the Guinea-pig, *Am. J. Anat.* 12: 207, 1912.
18. Homans, J.: The Study of Experimental Diabetes in the Canine and Its Relation to Human Diabetes, *J. Med. Res.* 33: 1, 1915.
19. Copp, E. F. F., and Barclay, A. J.: The Restoration of Hydropically Degenerated Cells of the Pancreatic Islands in Dogs under Insulin Treatment, *J. Metabolic Research* 4: 445, 1923.
20. O'Leary, J. L.: An Experimental Study of the Islet Cells of the Pancreas in Vivo, *Anat. Rec.* 45: 27, 1930.
21. Hanseman, D.: Die Beziehungen des Pankreas zum Diabetes, *Ztschr. f. klin. Med.* 26: 191, 1894.
22. Nicholls, A. G.: Simple Adenoma of the Pancreas Arising From an Island of Langerhans, *J. Med. Res.* 8: 385, 1902.
23. Ssobolew, L. W.: Ueber die Struma des Langerhans'schen Inseln der Bauchspeicheldrüse, *Virchows Arch. f. path. Anat.* 177: 123, 1904.
24. Herxheimer, G.: Weitere Untersuchungen am Pankreas von Diabetikern. *Verhandl. d. deutsch. path. Gesellsch.* 9: 263, 1905-1906.
25. MacCallum, W. G.: Hypertrophy of the Islands of Langerhans in Diabetes Mellitus, *Am. J. M. Sc.* 133: 432, 1907.
26. Dubreuil, G., and Anderodias: Îlots de Langerhans chez un nouveau né, issu de mère glycosurique, *Compt. rend. Soc. de biol.* 83: 1490, 1920.
27. Warren, S.: Adenomas of Islands of Langerhans, *Am. J. Path.* 2: 335, 1926.
28. Gray, S. H., and Feemster, L. C.: Compensatory Hypertrophy and Hyperplasia of the Islands of Langerhans in the Pancreas of a Child Born of a Diabetic Mother, *Arch. Path.* 1: 348, 1926.
29. Harris, S.: Hyperinsulinism and Dysinsulinism, *J. A. M. A.* 83: 729, 1924.
30. Wilder, R. M., Allan, F. N., Power, M. H., and Robertson, H. E.: Carcinoma of the Islands of the Pancreas, Hyperinsulinism and Hypoglycemia, *J. A. M. A.* 89: 348, 1927.
31. Howland, G., Campbell, W. R., Maltby, E. J., and Robinson, W. L.: Dysinsulinism, Convulsions and Coma Due to Islet Cell Tumor of the Pancreas. With Operation and Cure, *J. A. M. A.* 93: 674, 1929.
32. Brunschwig, A.: Large Islet Cell Tumor of the Pancreas, *SURGERY* 9: 554, 1941.
33. Frantz, V. Kneeland: Tumors of Islet Cells With Hyperinsulinism; Benign, Malignant and Questionable, *Ann. Surg.* 112: 161, 1940.
34. Duff, G. L.: The Pathology of Islet Cell Tumors of the Pancreas, *Am. J. M. Sc.* 203: 437, 1942.

35. Whipple, A. O., and Frantz, V. Kneeland: Adenoma of Islet Cells With Hyperinsulinism, *Ann. Surg.* 101: 1299, 1935.
36. O'Leary, J. L., and Womack, N. A.: Adenoma of Islands of Langerhans, *Arch. Path.* 17: 291, 1934.
37. Laidlaw, G. F.: Nesidioblastoma, Islet Tumor of Pancreas, *Am. J. Path.* 14: 125, 1938.
38. Bensley, R. R.: Structure and Relationships of the Islets of Langerhans, Harvey Lecture, Philadelphia, 1914-1915, J. B. Lippincott Company.
39. Grauer, T. P.: Regeneration in Pancreas of Rabbit, *Am. J. Anat.* 38: 233, 1926.
40. Mann, F. C.: Effects of Complete and Partial Removal of the Liver, *Medicine* 6: 419, 1927.
41. Bodansky, M.: The Production of Hypoglycemia in Experimental Derangements of the Liver, *Am. J. Physiol.* 66: 375, 1923.
42. Underhill, F. P.: Studies in Carbohydrate Metabolism, *J. Biol. Chem.* 10: 159, 1911-1912.
43. Sprague, R. G.: Effects of Chronic Experimental Liver Damage on Blood Sugar Response to Insulin, *Am. J. Physiol.* 110: 488, 1934.
44. Houssay, B. A.: What We Have Learned From Toad Concerning Hypophyseal Functions (Dunham Lecture) *New England J. Med.* 214: 913, 1936.  
Idem: Hypophysis and Metabolism (Dunham Lecture), *New England J. Med.* 214: 961, 1936.
45. Young, F. G.: Permanent Experimental Diabetes Produced by Pituitary Injections, *Lancet* 233: 372, 1937.
46. Long, C. N. H., and Lukens, F. D. W.: The Effects of Adrenalectomy and Hypophysectomy Upon Experimental Diabetes in the Cat, *J. Exper. Med.* 63: 465, 1936.
47. Womack, N. A.: Hypoglycemia, *SURGERY* 2: 793, 1937.
48. Wilder, R. M.: Hyperinsulinism (Colver Lecture), *Internat. Clin.* 2: 1-18, 1933.
49. Harris, S.: Gastrointestinal Manifestations of Hyperinsulinism, *Am. J. Digest. Dis. & Nutrition* 2: 557, 1935.
50. Bickel, G.: Painful Abdominal Phenomena in Hypoglycemia, *Arch. d. mal. de l'app. digestif* 24: 953, 1934.
51. Whipple, A. O.: The Surgical Therapy of Hyperinsulinism, *Jour. Internat. de Chirurgie* 3: Tome III, 1938.
52. Dunn, J. S., Sheehan, H. L., and McLetchie, N. G. B.: Necrosis of Islets of Langerhans Produced Experimentally, *Lancet* 1: 484, 1943.
53. Brunschwig, A., Allen, J. G., Owens, F. M., and Thornton, T. F.: Alloxan in the Treatment of Insulin Producing Islet Cell Carcinoma of the Pancreas, *J. A. M. A.* 124: 212, 1944.  
Brunschwig, A., and Allen, J. G.: Attempted Chemotherapy of Insulin Producing Islet Cell Carcinoma in Man, *Cancer Research* 4: 45, 1944.

# THE ENDOCRINOLOGIC ASPECTS OF TUMORS OF THE PINEAL GLAND

LEO M. DAVIDOFF, M.D., F.A.C.S.,\* BROOKLYN, N. Y.

*(From the Jewish Hospital of Brooklyn)*

## INTRODUCTION

THE pineal body was probably one of the earliest members of the endocrine series to be considered a glandular structure. In the second century Galen (quoted by Rowntree) stated: "It is in substance glandular. It was devised for the same purpose as other glands of the body." However, in spite of the extraordinary advances in the entire subject of endocrinology in the last few decades, the mystery of the pineal gland has remained unsolved. Even the question of its glandular nature, in spite of Galen's self-assurance, is to this day still a subject for debate. Experimental data are confusing and contradictory. The unique histologic appearance of this structure makes arguments by analogy with other glands of little value. Studies of pathologico-clinical states, especially tumors, which frequently have served to elucidate the normal function of an organ, have in the case of the pineal body appeared only to add to the confusion. With personal experience which includes five cases of tumor in the region of the pineal gland, I can offer no additional facts to the existing mass of material already in the literature. Indeed, there would be no excuse for this presentation if I were to accept a pronouncement published as recently as June, 1943, by Russell and Sachs: "This study offers no support for the concept that the pineal body is some form of endocrine gland." However, it is too simple to conclude that an organ has no function simply because we are unable to demonstrate what this function is. Too many glints of light from behind the curtain and too many intriguing fragments of unexplained data exist to allow one to be satisfied with a final judgment of a negative nature in this matter.

## DEVELOPMENT AND STRUCTURE

In the human embryo, according to Bailey, the pineal gland first makes its appearance during the fourth or fifth week as an outpocketing of the roof of the diencephalon. In front of this a second part, consisting of a cell mass, appears, according to Krabbe. As the fetus develops, the cell mass enlarges and the fold becomes deeper but the two are separated by a connective tissue wall. The cavity in the fold is closed

\*Chief, Department of Surgery, and Attending Neurological Surgeon.

Received for publication, Oct. 2, 1943.

after the sixth fetal month. After this, the cells, which up to now have been round and undifferentiated, begin to enlarge with larger but paler nuclei containing less chromatin than before. This differentiation takes place in a scattered manner throughout the gland and continues to the end of the first year of extrauterine life. By this time the gland has taken on essentially the appearance of that of the normal adult in that it consists mostly of islands of these large cells surrounded by smaller cells with darker nuclei, among which a few scattered connective tissue fibers are found. The origin and function of these two types of cells are still the subject of controversy. Some authors believe that certain granules in the large cells indicate a secretory character, while Hortega thinks these granules are merely blepharoplasts. Nageotte, on the other hand, is convinced that gliosomes in the smaller cells are indicative of a secretory character. The origin of the latter cells is also disputed. Globus and Silbert, for example, consider them to be of mesenchymal origin, capable of differentiating into fibroblasts. Horrax and Bailey, on the other hand, believe them to be of neuroectodermal origin.

#### FUNCTION

*Experimental Data.*—Outside of certain Australian lizards in which the pineal gland has become highly specialized as a centrally placed rudimentary third eye, the function of the pineal gland has not yet clearly been defined. Speculation in the ancient world as by Galen was already mentioned, and in more recent times, the philosopher, Descartes, considered it as the seat of the soul. Modern experimental efforts to elucidate the function of this body have consisted of extirpation and transplantation experiments as well as feeding and parenteral administration of various forms of extract of the pineal gland.

*Pinelectomy.*—About nine years ago Andersen and Wolf analyzed the reports in the literature on pinealectomies done in various experimental animals, including rats, rabbits, dogs, chicks, and guinea pigs. Experiments were reported in all these animals with negative results by some workers and positive results by others. The positive results, when they occurred, were reported most commonly to be "premature developments of secondary sex characters in the male, enlargement of the gonads, overgrowth of the body, and obesity." After critically analyzing all these data, the previously named authors were inclined to be skeptical about these results and felt that the data submitted were not sufficient to justify the conclusions reached.

*Feeding Experiments.*—Rowntree reviewed the experiments reported by McCord, consisting of feeding fresh pineal glands to 400 young animals which he claimed caused early precocity and adiposity. Hoskins, on the other hand, found such feeding experiments to result in no changes whatever.



*Pineal Implants.*—In implantation of pineal glands, reviewed by Rowntree, Kozelka showed negative results in chicks, whereas Dubowik found increased rate of growth in rabbits. Lahr showed some retardation in the gonadal development in both male and female rats but no influence upon the body growth.

*Injection of Pineal Extract.*—No definite results of pineal extract injections had been demonstrated until Engel appeared to have found an antagonism of the pineal extract toward the growth hormone of the anterior lobe of the pituitary, as well as toward those pituitary hormones affecting luteinization and maturation of the ovarian follicles. Rowntree furthermore called attention to McCord's paradox, namely, that, according to the reports in experimental literature, extirpation of the gland leads to precocity of development, while the administration of pineal gland in excess leads in the young to eventually the same result by "hastening growth and sexual maturity."

In view of all this confusion, Rowntree and his co-workers introduced a new factor in the injection experiments. They tested the effect of pineal gland extract not only on the individual animals receiving the injections intraperitoneally, but also on the offspring of successive generations of parent rats. At the time of their report, five generations of pineal strain of rat had been under observation. In the first generation no effect was apparent other than moderate loss of weight and indication of excess sex excitation and early breeding. In the second generation, definite retardation of growth with mild precocity of gonadal development occurred. In the third to the fifth generation, changes along the same lines but much more clearly evident were seen, both in the retardation of growth and in the acceleration of gonadal and bodily development, leading them to coin the designation "precocious dwarfism," that is to say animals dwarfed physically but showing relative genital precocity. The dwarfed stature of these animals is permanent, but though small in size, they show an acceleration in the opening of their ears, the eruption of their teeth, the appearance of fur, the opening of their eyes, the descent of the testes, or the opening of the vagina. The average young rat of the fifth generation under pineal treatment is described as less than one-half the normal in size with both gonadal and bodily development occurring precociously. The penis particularly is described as relatively large compared to the body size; the teeth are erupted early and the eyes open in less than one-half the normal time. The animals, however, are physically weak, irritable, and nervous. The studies of Rowntree and his co-workers on many hundreds of rats are impressive not only in that they show an amplification of biologic effect in succeeding generations, but also in that these effects strongly suggest the endocrine character of the pineal glands in these animals. Their results are, nevertheless, difficult to translate into clinical terms. However, they suggest that the syndrome of Pellizzi, *macrogenitosomia praecox*, is an expression of *hyperpinealism*.

## CLINICAL DATA FROM PINEAL TUMOR CASES

Patients with tumors occurring in the region of the pineal gland as reported in the literature have either shown no endocrinologic disturbances whatever or they have shown precocious pubertal development when the tumors affect young children, especially males. This syndrome described by Pellizzi is called *macrogenitosomia praecox* or *pubertas praecox*. Since it is the purpose of this communication to present only the endocrinologic aspects of tumor of the pineal gland, the five cases in my personal experience can be of little significance here except for the single case in which the previously named syndrome was present. The other four cases were those of two males and two females past the age of puberty who showed the classical neurologic signs of obstructive hydrocephalus with increased intracranial pressure and inability to rotate the eyes upward, which leads to a localization of a tumor mass in the region of the quadrigeminal plate in the neighborhood of the pineal gland. The fifth case was that of a 9-year-old boy with the syndrome of *macrogenitosomia praecox* which will be briefly presented here.

## CASE REPORT

F. H. (N. I. No. 30702), male, 9 years of age, was admitted to the Neurological Institute of New York Oct. 23, 1936.\*

*Present Illness.*—The patient was reported to be a normal healthy child until 9 or 10 months prior to admission, that is, January or February, 1936, at which time he began to have what at first was considered hoarseness but was later recognized as a distinct change in his voice, such as usually accompanies puberty. Within a short time thereafter, he developed pubic and axillary hair and rapid enlargement of both the penis and testicles. In March it was noted that he became mature-looking with a tendency to growth of a beard and soon thereafter he began to show some unsteadiness of gait. By May of 1936 he had gained twenty pounds since the onset of his illness. During the spring term at school, he began to show a distinct slump in his scholastic standing. By September, 1936, evidence of increased intracranial pressure was first noted in that he began to complain of severe frontal headache associated with vomiting, which was projectile in character. He also began to complain of double vision and his mother noted a strabismus which appeared about this time.

*Physical Examination.*—Examination revealed a 9-year-old boy acutely ill but presenting a most unusual physical appearance. He showed a relatively heavy growth of hair on the face as well as in the axillae and over the pubis and extremities. His "Adam's apple" was prominent and his voice had a distinctly adult low register. Although his height was compatible with his age, his penis and testicles were about average normal adult in size. No tumor of either testicle was present. Neurologically he showed bilateral papilledema with exudate and hemorrhages and pupils that were dilated and fixed to light and accommodation. There were left internal strabismus and right central facial paresis. The remainder of the neurologic examination was negative.

Laboratory findings were within normal limits. Roentgenograms of the skull showed only a calcific shadow of the pineal gland which, though somewhat unusual at 9 years of age, was not indicative of a tumor in this region.

\*Grateful acknowledgment is hereby made to Dr. Tracy J. Putnam, Director, New York Neurological Institute, for permission to utilize this material.

He was operated upon Oct. 27, 1936, when a tumor of the pineal gland was revealed and part of it removed for examination. He was then given 3,000 roentgens through the open wound in the operating room, after all the tissues except the tumor had been carefully shielded by sterile lead sheeting. The patient recovered from the operation and signs of increased intracranial pressure were considerably improved. Unfortunately, during the night following the operation, he tore off the dressing and inserted his fingers into the wound. This was followed by an infection which gradually spread to involve the meninges and he died of meningitis Dec. 29, 1936.

*Post-Mortem Examination.\**—The examination unfortunately was limited to the head only. This revealed, in addition to the infected wound and meningitis, a large tumor, best seen on sagittal section of the brain, measuring 5.3 by 5.2 cm. in diameter, occupying the upper one-half of the midbrain. The pineal gland was not discernible. The tumor compressed the anterior medullary velum and the anterior portion of the cerebellar vermis, the anterior surfaces of the cerebellar hemispheres, the dorsal aspect of the pons, the splenium of the corpus callosum, and the fornices (see Fig. 1). The tumor compressed the third ventricle posteriorly. The hypothalamus was distorted and foreshortened anteroposteriorly but was not directly impinged upon.



Fig. 1.—Sagittal section of brain showing large tumor in region of pineal.

Microscopically the tumor was found to be quite cellular, fairly vascular, with areas of hemorrhage and focal necrosis. The tumor cells were loosely arranged in small, irregular clusters which were separated by a vascular network and single or multiple rows of slender elongated cells. The predominating cell was irregular, polygonal, rarely rounded, occasionally having small processes. The cell cytoplasm was scanty, but the nuclei were large and round, oval, or slightly irregular with a moderate amount of finely granular chromatin and frequently a prominent nucleolus. Mitotic figures were commonly seen. Another type of cell less frequently encountered in the tumor was very large and irregular with abundant cytoplasm and large hyper-

\*The author is indebted to Dr. Abner Wolf for the data concerning the pathologic appearances.

chromatic, often multiple, nuclei. The elongated cells, already mentioned, formed occasional bands of considerable width. Areas of necrosis, hemorrhage, and calcium deposition require no special description (see Fig. 2).

The pathologist concluded that the tumor was a complex neoplasm which he classified as a chorioepithelioma. Urine obtained by catheter post mortem gave a positive Friedman test. He was of the opinion that, in spite of the limited examination, the tumor was primary in the pineal region, rather than metastatic from somewhere else.

It is of passing interest perhaps that Bochner and Searf, who reviewed the literature up to 1938, were able to find only one recorded case of chorioepithelioma of the pineal gland, reported by Askanazy.



Fig. 2.—Photomicrograph ( $\times 60$ ) showing general character of tumor.

#### COMMENTS

Although the picture of macrogenitosomia praecox is usually associated in the minds of most observers with a tumor of the pineal gland and usually the character of the tumor is considered that of a teratoma, these cases are nevertheless very rare. In 1925, Horrax and Bailey found only four cases in the literature and were able to add two more from Dr. Cushing's enormous material. In that report, however, they called attention to the case of Klapproth which was that of a boy of 15 years with a teratoma of the pineal gland who showed sexual infantilism rather than precocity. In 1928, Horrax and Bailey again added one more case of a probable pineal teratoma in which the patient showed pubertas praecox, but in the same article they reported another with an even more remarkable premature puberty in which the pineal was within normal limits, and a large tumor in the third ventricle histologically diagnosed as ganglioneuroma was found at operation and confirmed at

post-mortem examination. In 1938, Bochner and Searf argued that the teratomatous tumors of the pineal gland may produce a premature sexual development in their victims by an effect similar to the stimulation of the ovaries in immature rabbits by urine obtained from pregnant women. They found some confirmation in this view in that the Aschheim-Zondek test is positive in males with teratomatous tumors of the testicles. Indeed, my own case illustrated the presence of a positive pregnancy test with a pineal tumor. Unfortunately, Bochner and Searf's theory is exploded in the evidence presented by their case which was that of a 9-year-old boy who died of a teratomatous tumor of the pineal body and who showed no evidence of pubertas praecox. Moreover, pubertas praecox associated with a teratoma of the pineal gland in a female child is practically unknown, yet the pregnancy test is positive only when made on immature female animals.

#### DISCUSSION

The most widely accepted theory of the function of the pineal gland, as stated by Marburg, is that its secretory activity during the early years of life inhibits a development of puberty and that at the time of puberty the gland undergoes involution which thus removes its inhibitory effect and allows sexual development to take place. It was believed that the cases of macrogenitosomia praecox in which a large tumor destroying the pineal gland is present in early life might support this theory. However, we have Horrax and Bailey's case of a boy with a normal pineal gland and a tumor in the third ventricle not of pineal origin presenting the syndrome of premature puberty, and a similar case was reported by Schmalz. We have, moreover, the case reported by Horrax and Bailey in which the tumor of the pineal gland, which was associated with macrogenitosomia praecox, was not a teratoma but a pinealoma, reproducing in great abundance mature pineal tissue. Here it might be argued that even if the pineal gland were destroyed by the tumor, the tumor itself would more than supply the secretion of the gland. It may indeed be considered as evidence in this case that secretion of the pineal gland in excessive amounts initiates puberty rather than inhibits it. Further clinical support is lent to this theory by the prepubertal cases in which tumors other than teratoma or pinealoma occur and are not accompanied by premature puberty, for in these instances it may be argued the gland is actually destroyed and its secretion interrupted, and therefore no sexual changes accompany the tumor. A destructive tumor of the pineal gland associated with actual infantilism in the case reported by Klaproth, already mentioned, may be further evidence to point in this direction. Still another case supporting the point of view that the pineal secretion initiates puberty is that reported by Zandren, who described a case of infantilism that showed at necropsy no trace of the pineal body, even though this structure was searched by careful serial sections of the entire region.

How are we then to explain those teratomatous tumors which have been most commonly accompanied by premature puberty, since these tumors also destroy the pineal gland? Globus and Silbert believe that the marked variability in the histologic appearance of pineal tumors giving rise to a great variation in designation may be due to the different embryologic stages of the pineal body itself from which the tumors develop. They thus imply that even though tumors in the literature are often called "teratomas," they nevertheless are frequently pineal in origin. In view of the fact that these complex tumors may, therefore, originate from the pineal gland in its various stages of development, one might then assume some specific quality inherent in them, namely, a pineal-like secretion produced in sufficient amounts to initiate early puberty.

A further difficulty arises in attempting to explain on the basis of this theory Horrax and Bailey's case with a classical picture of macrogenitosomia praecox in a child with an apparently normal pineal and a large ganglioneuroma within the third ventricle. Here a possible explanation may exist in that the patient was demonstrated to have a normal-sized pineal gland which for some reason, perhaps associated with the abnormal hydrodynamics within the skull, was led to secrete abnormal quantities of hormone, producing an early development of puberty.

#### CONCLUSIONS

It is obvious from the foregoing that the problem of the pineal body is by no means solved. Even the question as to whether it is a gland or not is not wholly clear. On the other hand, it would seem to be possible to deduce, with less violence to the facts than by any other theory, from data obtained from the study of pineal tumors, that the pineal body is a gland of internal secretion with a hormone which apparently initiates puberty. This viewpoint moreover is supported by the most conclusive experimental data available up to this point, namely, that of Rowntree and his associates.

#### REFERENCES

- Andersen, D. H., and Wolf, A.: Pinealectomy in Rats, With Critical Survey of Literature, *J. Physiol.* 81: 49, 1934.  
 Askanazy, M.: Teratom und Chorionepitheliom der Zirbel, *Verhandl. d. deutsch. path. Gesellsch.* 10: 58-76, 1906.  
 Arey, L. B., and Bailey, P.: *Special Cytology*, ed. 2, New York, 1932, Paul B. Hoeber, Inc., p. 789.  
 Bochner, S. J., and Scarf, J. E.: Teratoma of the Pineal Body, *Arch. Surg.* 36: 303, 1938.  
 Dubowik, J. A.: Versuch einer hormonalen Beschleunigung des Wachstums junger Tiere, *Endocrinologie* 11: 15, 1932.  
 Globus, J. H., and Silbert, S.: Pinealomas, *Arch. Neurol. & Psychiat.* 25: 937, 1931.  
 Hoskins, R. G.: *The Tides of Life*, New York, 1933, W. W. Norton & Co., Inc.  
 Horrax, G., and Bailey, P.: Tumors of the Pineal Body, *Arch. Neurol. & Psychiat.* 13: 423, 1925.  
 Horrax, G., and Bailey, P.: Pineal Pathology, *Arch. Neurol. & Psychiat.* 19: 394, 1928.

- Hortega, del R.: *Constitucion histologica de la glandula pineal*, Arch. de neurobiol. 3: 359, 1922.
- Klaproth, W.: *Teratom der Pineal Combiniert mit Adenom*, Centralbl. f. allg. Path. u. path. Anat. 32: 617, 1921.
- Kozelka, A. W.: *Implantation of Pineal Glands in Leghorn Fowl*, Proc. Soc. Exper. Biol. & Med. 30: 842, 1933.
- Krabbe, K. H.: *Histologische und embryologische Untersuchungen über die Zirbeldrüse des Menschen*, Anat. Hefte 54: 191, 1916.
- Lahr, E. L.: *Quoted by Rowntree*, Tr. Kansas Acad. Sc. 35: 1932.
- Marburg, O.: *Zur Kenntnis der normalen und pathologischen Histologie der Zirbeldrüse: Die Adipositas Cerebralis*, Arb. a. d. neurol. Inst. a. d. Wien. Univ. 17: 217, 1909.
- McCord, C. P.: *The Pineal Gland*, Surg., Gynec. & Obst. 25: 250, 1917.
- Nageotte: *Quoted from Bailey*.
- Rowntree, L. G.: *The Pinal Gland*, in Tice, *Practice of Medicine*, vol. 8, chap. 8, Hagerstown, Md., 1938, W. F. Prior, Company, Inc., p. 535.
- Russell, W. O., and Sachs, Ernest: *Pinealoma: A Clinicopathological Study of Seven Cases With a Review of the Literature*, Arch. Pathol. 35: 869, 1943.
- Schmalz: *Ueber einen Fall von Hirntumor mit Pubertas praecox*, Beitr. z. path. Anat. u. z. Alleg. Path. 73: 168, 1924. (*Quoted from Horrax and Bailey*, 1928.)
- von Engel, P.: *Ueber die antigonadotrope Wirkung des Epiphysans*, Wien. klin. Wehnschr. 48: 1160, 1935.
- Zandren: *A Contribution to the Study of the Function of the Glandula Pinealis*, Acta med. Scandinav. 54: 323, 1921.

## Book Reviews

---

**Medical Physics.** By Otto Glasser, Editor-in-Chief, with 23 Associate Editors. Pp. 1744. Chicago, 1944, The Year Book Publishers, Inc.

The only appropriate description for this volume is monumental. It represents a great contribution to medical science literature in any language, and is one of a very few of comparable importance of American origin. More than 300 sections, each prepared by recognized original contributors to the numerous fields, present the various aspects of medical physics in a manner such as to make the volume a veritable mine of information and critical evaluation. It is at once indispensable for every scholarly clinician, a source book for investigators, and a handbook for the study of principles of physics and physical chemistry as they apply to biology and medicine. The title is not quite broad enough, unless one includes under "medical" everything fundamental to it, which the editors have obviously done. The volume actually represents a compendium of knowledge about biophysics in general, with special reference to medical problems.

The editors deserve nothing but praise for the useful work they have done in bringing so nearly all that is basic and useful in physics and physical chemistry into one volume for ready consultation. There are, of course, defects in the organization and presentation. There is lack of uniformity in practice about citation of references. The physics of gas flow in respiration is not adequately treated in the normal and pathologic subject. The problem of atelectasis is described without reference to alternative mechanisms of production, which in the opinion of many recent authors are more frequently causal than the one described. There are other instances of this type, and the editors will undoubtedly seek to improve the volume in many details in future editions, but the reviewer's opinion is that considering the scope of the work the defects are surprisingly few and the merits exceedingly great. As noted, the only principal improvement urgently indicated is a fuller bibliography. Aside from this a careful restudy of completeness of coverage of the various fields by the editors and their expert consultants is desirable.

The present volume serves a very real need and should be in the library of every physician with scholarly interests, as well as in every group medical library. The publishers are to be congratulated for their courage in risking the publication of this valuable book and in the generally excellent workmanship it embodies.

---

**Intracranial Arterial Aneurysms.** By Walter E. Dandy. Pp. 147. Ithaca, N. Y., 1944, Comstock Publishing Company, Inc.

This monograph consists of a systematic and comprehensive presentation of a difficult and little known clinical entity—intracranial arterial aneurysms—based on a study of 108 patients with 133 aneurysms. The subject is introduced by a general discussion of the incidence, types, symptoms and signs, and diagnostic procedures of intracranial arterial aneurysms. In the second chapter the cases are considered from the standpoint of an anatomic classification. A detailed analysis of each group is included in tabular form. The third chapter, by Dorcas Hager Padgett, is devoted to the embryology and anatomy of the circle of Willis. In the fourth chapter the methods of preoperative ligation of the carotid and vertebral



arteries are described. The last chapter contains a discussion of the surgical treatment and operative results. Dandy was able to report cures in twenty patients in the series. An appended bibliography, tabulation of the series of cases, and perspicuous illustrations suggest the intensive research required in the preparation of this volume. The lack of an index is probably an intentional and perhaps not a serious omission, since the subjects are clearly indicated in the table of contents.

This compendium fills a definite need "in a seemingly barren field," which has actually proved, "with increasing confidence in diagnosis and with the correlated surgical follow-through" to be quite common, as the author has suggested in his preface.

---

**The Year Book of General Surgery.** Edited by Evarts A. Graham, A.B., M.D., Professor of Surgery, Washington University School of Medicine; Surgeon-in-Chief of the Barnes Hospital and of the Children's Hospital, St. Louis. Ed. 1. Pp. 736, with 270 illustrations. Chicago, 1944. The Year Book Publishers, Inc. \$3.

*The Year Book of Surgery* is as large as in previous years and follows the same general scheme of treatment of a very broad subject matter. The items discussed under the caption of Military Surgery have increased in number, and throughout the volume emphasis has been given to the effects of trauma.

The editor states in the preface, "One of the regrettable casualties of war is its effect on scientific progress. What advance in science occurs is concerned chiefly with attempts to aid the actual conduct of fighting. There is no encouragement to pursue that sort of investigation which will make for better living or better health. The more nearly total the war becomes, the more striking will be its inhibiting effect on research that is unconnected with military affairs. Now in the fifth year of this total war it is apparent to anyone who reads the current literature that the amazing speed of scientific progress which characterized the last 50 years has been retarded to an appalling degree. How long this wave of depression will last cannot be foreseen."

There are new ideas and new procedures outlined in the 1943 Year Book and this rather gloomy note of the editor may appear a bit unduly pessimistic. As the editor implies, during time of war, all research, save that with a definite war-linked interest, of necessity comes to a virtual standstill. And it is through original experimental research that new facts are multiplied and the complexion of old and difficult problems changed.

The pertinent comments of the editor upon the publication of abstracts of papers are not as numerous as in some of the previous Year Books. Nevertheless, the volume is a good index of the surgical literature and a useful by every surgeon.

there is any need to be. This tendency is unfortunately increased by a small number of chapters that seem entirely out of place.

There are many illustrations throughout the book, but most of them are of poor quality so that they do not have the value they should have. Reproductions of roentgen films, however, are satisfactory.

In contrast to the faults which have been listed, there are many excellent chapters by celebrated authors such as Denny-Brown, Cobb, Gillies, Smith-Petersen, Watson-Jones, and others. The material presented by this group is well organized and of great value to those in civilian practice quite as much as to those in the Armed Forces. A most interesting section is given to immersion-foot and allied ailments.

The volume contains some material that is not of much value, but this is more than outweighed by the large number of excellent sections included.

---

**Pain Mechanisms.** By W. K. Livingston, Lieutenant Commander, M.C., U.S.N.R., Assistant Clinical Professor of Surgery, University of Oregon Medical School, Portland, Ore. Ed. 1, Pp. 253, with 26 illustrations. New York, 1943, The Macmillan Company. \$3.75.

This book consists of three parts. The first part is a discussion of the anatomy and physiology of pain. In this, the author lays the foundation for the main theme of the book, namely that intractable pain such as causalgia, other post-traumatic pain syndrome, low back disability, neuralgias, and phantom limb pain may be due to an internuncial pool of neurons in the cord. He infers that through increase in the phenomenon of facilitation and decreased inhibition in this internuncial pool, both being functions of this group of cells, ordinary nonpainful afferent impulses become painful.

The second part is concerned with the clinical syndromes of causalgia, post-traumatic pain syndromes, low back disability, facial neuralgias, chronic and phantom limb pain. This is the most valuable part of the book. The discussion of these conditions is good; the author has obviously had a large experience and many cases are described. Many patients received lasting relief from novocain injections. The possibility that when novocain injections are followed by lasting relief it may be due to suggestion is discussed but dismissed by the author. He is convinced that it is a mistake to assume that a certain pain syndrome must represent an obsession or be of purely psychic origin, simply because its manifestations do not conform to what we have been taught about the anatomy and physiology of peripheral nerve pathways. He believes that it is equally foolish to discredit the results of procedures such as periarterial sympathectomy and novocain injection on the ground that their mode of action is obscure.

The third part of the book is called Interpretations. It is composed of chapters on protopathic pain, hyperalgesia, the sympathetic component, and the vicious circle.

Protopathic pain is a discussion of Head's experiments and those of others who confirmed or refuted Head's notion of a special, primitive type of nerve to account for protopathic pain. He finally concludes that anything that might act to disturb the normal pattern of impulses anywhere along their route from the periphery to the perceptual centers might lead to an unusual pattern of central excitation, and hence produce abnormal changes in sensory experience. A pathologic state of the internuncial pool within the spinal cord is suggested as one of the sites at which this distortion of sensory impulses might occur.

In the chapter on hyperalgesia, after discussing experimental work of various investigations on hyperalgesia, the author concludes that hyperalgesia may be due to modification of impulses anywhere between the periphery and sensorium, such as elaboration in the skin of some chemical substance which acts to increase the

sensitiveness of the skin locally, withdrawal of a part of the impulses which customarily constitute the composite of impulses underlying normal sensations derived from the skin, distortion of the intraneural pattern which results in fibers establishing new connections in regenerated nerves, abnormal sensations of the cells of the posterior horns of gray matter, lesions of the posterior columns, injuries of the brain in the region of the thalamus, or alteration in the status of the internuncial pool, the receiving station at the cord level

Under sympathetic component the author points out that relief of causalgia cannot be due to section of afferent pain fibers in the sympathetic nerves, and that it is at least not always due to increased blood flow. Since elimination of either the trigger point or the sympathetic nerves alone may not give relief of the causalgia, he assumes that neither is the sole cause of the causalgic state. His assumption is that the barrage of abnormal impulses from an injured nerve acting on the internuncial pool of neurons in the cord disturb its normal functioning and this, in turn, disturbs the functioning of the sympathetic nerves and peripheral somatic nerves to produce peripheral changes from which abnormal afferent impulses arise to add themselves to those of the trigger point to sustain and augment the central activity

In the chapter on the vicious circle the author attempts to explain his concept of the vicious circle in causalgic states, and to compare it with the concept of the vicious circle as it is utilized by the psychiatrist to explain tension states. Essentially the difference he recognizes in the two is that psychic irritants set up a disturbed center chiefly at higher or cerebral levels, while in the causalgic state the disturbed center is primarily at least in the internuncial pool of the cord.

An organic lesion at the periphery, involving sensory nerve filaments, may become a source of chronic irritation. Afferent impulses from this trigger point eventually create an abnormal state of activity in the internuncial centers of the cord gray matter. The internuncial disturbances, in turn, are reflected in an abnormal motor response from both the lateral and anterior neurons of one or more segments of the cord. The muscle spasm, vasomotor changes, and other effects which this central perturbation of function brings about in the peripheral tissues may furnish new sources of pain and new reflexes. A vicious circle of activity is created. Thus, an ever widening circle is set up and the advantage of treatment is obvious.

There are three reciprocating factors: the incoming impulses from the periphery; the internuncial pool activity, and the motor impulses from the lateral and anterior horn cells that are brought within the influence of the pool.

The author is congratulated upon writing a well arranged and interesting book about these baffling clinical entities. His concept of the internuncial pool is theoretical and may be rejected, but the book contains many interesting and valuable observations.

It could be read with profit by almost any physician but should be of special interest to neuropsychiatrists, surgeons, and psychologists.

# SURGERY

Vol. 16

SEPTEMBER, 1944

No. 3

## Original Communications

### MYOBLASTOMA\*

CHESTER W. HOWE, M.D., BOSTON, MASS., AND

LIEUTENANT COMMANDER SHIELDS WARREN, MEDICAL CORPS, U.S.N.R.

*(From the Pondville Hospital, Massachusetts Department of Public Health and the Laboratory of Pathology of the Harvard Cancer Commission)*

ONE of the less well-recognized tumors is the myoblastoma, whose type cell is the primitive precursor of striated muscle. Within the past few years we have encountered ten cases, five of which showed definite malignant properties; three of the latter metastasized to the lungs.

Since knowledge of the clinical behavior of these tumors is still scanty, it seems worth while to review that knowledge and to present the clinical and pathologic features exhibited by these cases. The tumor was first described by Abrikossoff<sup>1</sup> in 1926 as a tumor of myoblasts, occurring chiefly in relation to striated muscle. Some of the cases, as those of Keynes<sup>20</sup> and Dewey,<sup>14</sup> have been reported as rhabdomyoma. In 1933 Klemperer<sup>32</sup> reviewed the subject and collected forty-four cases, adding six new ones from his own material. Gray and Gruenfeld,<sup>24</sup> in 1937, published a topographic grouping of the cases then known and added five new ones, bringing the total to seventy-seven. In 1943, Horn and Stout<sup>26</sup> reported two cases and mentioned twenty-seven more in their material.

Myoblastoma must be differentiated from other primitive tumors of mesenchymal type on the one hand and from rhabdomyoma and rhabdomyosarcoma on the other hand. The two chief types of readily recognized striated muscle tumors are those occurring in voluntary and those occurring in cardiac muscle. Those arising from voluntary

\*This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the U. S. Navy. The opinions and views set forth in this article are those of the writers and are not to be considered as reflecting the policies of the Navy Department.

Received for publication, Feb. 4, 1944.

muscle and those striated muscle elements in teratoid tumors usually present elongate to banjo-shaped cells, with often longitudinal striations and sometimes cross striations. The type occurring in cardiac muscle is usually made up, at least in part, of very large,<sup>54</sup> rounded cells of so-called spider-web type with the striations arranged somewhat concentrically. The cardiac tumors are almost all congenital and benign.

The characteristic cell in myoblastoma is large, pale, polyhedral, and granular, frequently arranged in pseudo-alveolar fashion, although lumina are not formed (Fig. 1). Not infrequently, ribbonlike or irregular syncytial masses may occur. In both of these types of cells the cytoplasm is somewhat granular and resembles that of primitive myoblasts. Rarely, a few cross striations may be present (Abrikossoff<sup>1, 2</sup> reported them in two of his cases). The cytoplasm tends to be acidophilic and sometimes is vacuolated. It is quite possible, if one does



Fig. 1.—Gross specimen of primary tumor, Case 1.

not carry out stains for lipid, to mistake them for xanthoma cells. The nuclei are small as contrasted with the cytoplasm and vary a little in size; they may be vacuolated (Fig. 2). Mitotic figures are rare. Frequently cells contain multiple nuclei. A delicate connective tissue stroma supports either single cells or groups of cells. Often a definite capsule is present, but if it is absent, the tumor cells blend almost imperceptibly with the adjacent striated muscle.

Abrikossoff<sup>1</sup> originally distinguished four varieties of muscle tumor under the heading of myoblastoma: (1) Tumors composed of myoblasts completely devoid of striations; the pure myoblastoma. (2) Tumors with myoblasts similar to type 1 but showing infrequent longitudinal or cross striations or both, only imperfectly developed in the margins of cells. (3) Tumors with hypertrophic myoblasts, including some of great size (40 to 160 micra in length), frequently multinucleated and of syncytial type. Striation may be present in some,

especially in the peripheral zone of cytoplasm, but is absent from many. (4) Atypical myoblastic sarcoma; a polymorphous-celled tumor, in some areas frankly sarcomatous, in others showing more highly differentiated cells with well-defined longitudinal and cross striation.

In our opinion, Abrikossoff's<sup>1</sup> Group 4 cases are better included with the rhabdomyosarcomas and we have so diagnosed our own examples of the group. To avoid confusion in tabulating the reported cases, we have included those previously recorded as meeting the criteria for Abrikossoff's Group 4 as well as those falling in his first three groups.



Fig. 2.—Pleural metastases of myoblastoma, Case 1.

It is easy to determine the nature of this tumor when it occurs in contact with striated muscle and when scattered transitional cell forms exist. Such transition cells have been reported by Gray and Gruenfeld<sup>24</sup> (tumors of tongue) and by Grayzel and Friedman<sup>25</sup> in a tumor of the thoracic wall. While some authors<sup>13, 15</sup> illustrated apparent transition of the granular cells into striated cells, others<sup>32, 42, 48</sup> believe that these are probably erroneous interpretations. As has been pointed out by Klinge,<sup>33</sup> the occurrence of the tumor in regions where no striated muscles appear can be explained only on a dysontogenetic basis. It has been suggested<sup>42, 47</sup> that following trauma to striated muscle, granular degeneration might occur and excessive regeneration taking place in such injured fibers might lead to the development of neoplastic qualities.

The tumor is usually first noted as a small, yielding, nontender mass, often only 1 cm. or more in diameter. On section it is grayish pink

or whitish and as a rule fairly clearly demarcated, although it occasionally shows no definite border. Ulceration is rare and, indeed, there may be hyperplastic or neoplastic response of the overlying skin or mucous membrane. The great majority of these tumors are benign, but we, as others, have encountered malignant ones, which will be discussed later in this communication.

#### CASE HISTORIES

CASE 1.—M. V., a 36-year-old white American housewife entered Pondville Hospital, March 27, 1941, complaining of aching and swelling of the upper left arm of two and one-half months' duration. Examination showed a hard, movable, fusiform mass 4 cm. in diameter on the anterior aspect of the left shoulder at the level of the surgical neck of the humerus.

May 31, 1941, the mass was excised taking the overlying attached skin and subcutaneous tissue and some of the deltoid muscle fibers. Pathologic report on the specimen was "myoblastoma" (Fig. 1).

From August to December, 1941, she worked in an ammunition factory, and in common with other workers there developed what she called a "tetryl cold" and experienced nasal discharge, nosebleeds, headaches, yellow skin discoloration (perspiration stained clothes yellow), and a mild attack of diarrhea. At this time she experienced pain in the right shoulder.

Jan. 8, 1942, she appeared at Pondville Hospital Out Patient Clinic complaining of pain in the right shoulder, shin, and hip. Two months previously she had first noted an enlarging tumor mass in the right upper arm. Examination at this time showed a well-healed, postoperative scar with no recurrence on the left. In the right mid-humeral region there was a fusiform hard mass 5 cm. in diameter fixed to the underlying bone. Also, just medial to the right anterior superior spine of the ilium there was an indefinitely outlined, hard mass roughly 8 cm. in diameter, fixed and slightly tender. Skeletal x-rays showed slight rarefaction in the right humerus not typical of metastatic disease. No other bone pathology was found. The patient was given a course of deep x-ray therapy consisting of 2,000 r to the right humerus and 2,000 r to the right iliac crest region.

Feb. 5, 1942, she reappeared in the outpatient department on a stretcher with obvious severe pain in her right shoulder, right hip, and back. X-rays at this time showed metastatic disease in the fifth dorsal vertebra and in the left pubic bone. She was treated by deep x-ray therapy to the extent of 1,800 r distributed to the various painful areas.

During mid-February she developed numbness along the lower jaw on the right side, progressing to severe pain at the tip of the chin. X-ray pictures of the foramen ovale showed no evidence of bone metastases.

Blood studies showed a progressive anemia (normocytic) and a low white count. A bone marrow biopsy was essentially negative.

March 14, 1942, a fixed mass of fused lymph nodes 3 cm. in diameter was removed from high in the left axilla and was proved pathologically to be metastatic myoblastoma.

The patient had a constant temperature of about 100° F. and the pulse averaged 115. The pain increased and required large doses of morphine. X-ray checkup pictures showed advancing disease in the thoracic spine, left scapula, and left innominate bone. Additional x-ray therapy was given with only partial relief of pain. Extensive blood chemistry studies were carried out which served to throw no light on the nature of the disease. The pain increased, appetite failed, and the patient became bedridden. There was marked weight loss and she died on April 28, 1942.

Autopsy showed primary myoblastoma of the left deltoid region with multiple metastases to bones, pleura, lungs, axillary and tracheobronchial lymph nodes, liver, and adrenals. There was bilateral hydrothorax and the external surfaces of the lungs were studded with tumorous nodules (Fig. 2).

CASE 2.—O. S., a 64-year-old man, inmate of the Taunton State Mental Hospital, was admitted to Pondville Hospital for treatment of a small tumor on his tongue. Due to the patient's mental status, no history was obtained except the fact that he was a heavy pipe smoker.

Examination showed a granular lesion 7 mm. in diameter, firm and whitish, on the left side of the tip of the tongue. The teeth were ragged and foul. It was thought at the time that the lesion was of dental etiology. There were no palpable cervical nodes.



Fig. 3.—Myoblastoma of tongue.

July 1, 1940, partial glossectomy was done. The tumor of the removed specimen was 8 by 7 by 4 mm. and grayish white on cut section. Microscopically the picture was one of a type 2 myoblastoma.

The patient had an uneventful convalescence, and when last seen two years after operation was free from disease.

CASE 3.—L. F., a 17-year-old, single female, was first seen at the Westfield State Sanatorium in April, 1941, having had a previous excision of a tumor of the left buttock, elsewhere. She had a history of being in an automobile accident February, 1941, at which time she had received numerous contusions and abrasions to the body. Following this she complained of low back pain and was kept in bed four or five days. During this time she began to complain of a tender, painful swelling in the left buttock about the size of a small hen's egg. This grew and became more tender as a result of lying on it.



When first seen at Westfield, there was a scar 3 cm. in length just lateral to the crest of the ilium. The zone of the previous excision was widely excised, and the pathologic report was hemangioendothelioma. (These microscopic sections were not available to us for review.)

In January, 1942, on a follow-up visit, an egg-sized mass was found at the junction of the upper and middle thirds of the incision. This mass was slightly movable. It was again widely excised, and the pathologic report was myoblastoma (Fig. 5).

She was given x-ray treatment, totaling 2,500 r, directed to the tumor site in the left gluteal region.

She was followed regularly at the Westfield Out Patient Department, the last follow-up visit being in August, 1943, at which time there was no evidence of recurrent disease. She has had no menstrual period since the x-ray treatment and is suffering from hot flashes.

CASE 4.—A. K., an 81-year-old man was admitted to the Lowell General Hospital complaining of a tumor on the outer aspect of the lower part of the left thigh. He gave a history of having had a tumor excised from this area previously, June 12, 1941. Examination showed an ovoid tumor 6.2 cm. in diameter centering in the scar of the previous excision. Operative note: Under novocain anesthesia the old scar and tumor were excised. The tumor was somewhat adherent to the underlying fascia but was separated from it without difficulty, leaving a smooth clean base. The wound was closed with interrupted mattress silk sutures. The specimen consisted of the skin scar tissue with an ovoid, flesh colored tumor 6.2 cm. in diameter attached. The tumor consisted of an outer solid grayish-white zone and an inner soft degenerated zone. The pathologic report was myoblastoma. When last seen, approximately one year following excision, there was no evidence of recurrence.

CASE 5.—E. P., a 24-year-old male laborer, was admitted to Poudville Hospital, Dec. 11, 1941, for excision of a tumor on the left hand, noted two years previously on the palm over the flexor tendon of the index finger, which had gradually increased in size to become 2 cm. in diameter. A second smaller tumor appeared adjacent to it. Gradually these tumors became painful and caused contraction of the index finger.

Nov. 11, 1941, these masses were excised by his physician and diagnosed myoblastoma, malignant.

The examination on entry showed an enlarged right tonsil, cervical, axillary, and inguinal adenopathy, bilateral epitrochlear adenopathy, and a scar 7 cm. in length along the thenar eminence of the left hand.

Blood studies were within normal limits, and the serology was negative.

The epitrochlear node was excised for biopsy and proved to be hyperplastic. A roentgenogram of the chest was negative. The patient was discharged at his own request but delayed in returning. When he did return, there was increased thickening in the scar with a nodule 2 cm. in diameter at one end. The cervical, axillary, and inguinal adenopathy remained unchanged.

Jan. 26, 1942, re-excision of the tumor was done (Fig. 4). Since it was impossible to remove all the tumor by local excision, permission for an amputation was obtained, and Feb. 10, 1942, a partial amputation of the left hand, leaving the lateral two fingers, was done. Sections of this specimen revealed tumor at the margin of the incision. The wound healed by first intention. The left axillary nodes increased in size and number.

Feb. 24, 1942, the patient had an amputation of the lower one-third of the forearm with epitrochlear and axillary dissection. Fifty-two lymph nodes were

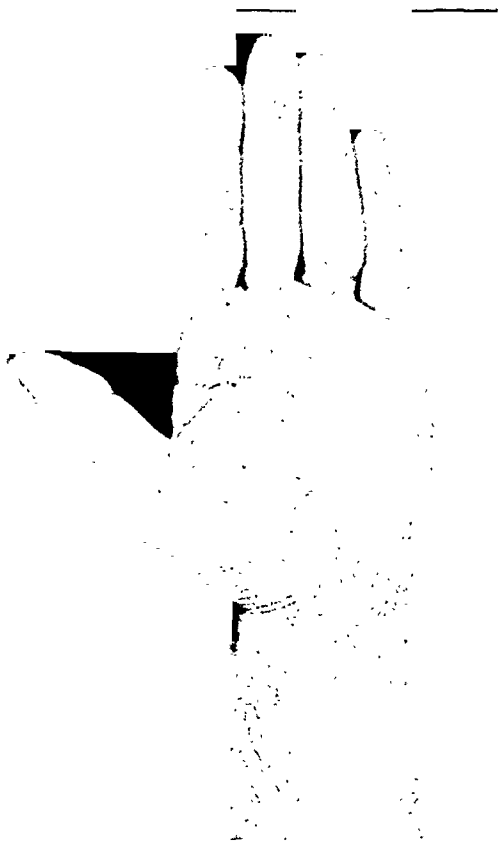


Fig. 4.—Recurrent tumor, Case 5.

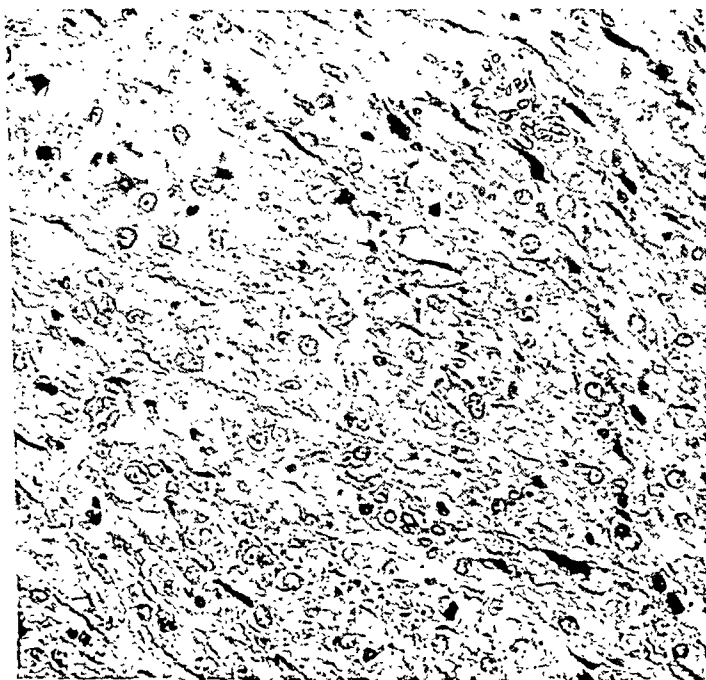


Fig. 5.—Myoblastoma, type 2 (Case 3). This field shows chiefly type 1 or granular cells. Phosphotungstic acid hematoxylin stain ( $\times 290$ ).

removed with the dissection, all of which showed hyperplasia but no evidence of tumor. The removed specimens showed firm, gray tissue in the scar. The overlying epithelium was normal. There were clumps of polyhedral cells with foamy cytoplasm and few mitoses. Some of the cells were in syncytial strands.

Five months later there was neither recurrence nor metastasis.

CASE 6.—A.K., a 52-year-old white married woman, struck her right thigh against a table and the following morning developed marked swelling at the site of the trauma. During the next few weeks a large, soft, fungating tumor appeared over the same area. This was thought to be a broken-down hematoma and it was opened by her physician releasing much bloody material. A biopsy was submitted to the Tumor Diagnosis Service and a diagnosis of myoblastoma was made. Six weeks later the patient was brought to the Huntington Hospital by her physician. At that time examination showed a tumor 10 cm. in diameter in the outer aspect of the central part of the right thigh extending deeply into the subcutaneous tissues with a fungating mass 4 cm. in diameter breaking through the skin. There were no palpable inguinal lymph nodes. X-ray showed a large infiltrating, soft tissue tumor occupying one-half of the outer aspect of the right thigh. An amputation was advised, but the patient refused both this and local excision. She returned home to her physician, and a course of deep x-ray therapy (dosage not available) was given, followed by regression of the tumor. An area of marked radiation reaction measuring 15 by 20 cm. persisted.

In November, 1937, a roentgenogram of the chest showed a small shadow in the right upper lobe which continued to enlarge on repeated examinations in spite of deep x-ray therapy. Information was received that the patient died on April 1, 1938, with lung metastases. The local lesion of the thigh was completely healed and the patient had previously been able to walk about.

CASE 7.—C.L., a 71-year-old white man entered the Huntington Memorial Hospital Oct. 14, 1941. He stated that he had noticed a small rough lesion on the inside of his right cheek for some time and that five weeks previously, it had suddenly developed into a rapidly enlarging tumor. Examination on entry showed him to be edentulous and wearing an upper and lower plate. There was a rubbery, pedunculated growth measuring 2 by 3 cm. springing from the right buccal mucosa 1 cm. inside the right commissure. It appeared very vascular and was oozing bright red fluid. There was some roughening and granulation over a small area just posterior to the site of the tumor. A firm node 1 cm. in diameter was palpable in the right submaxillary triangle adjacent to the border of the mandible.

Examination Oct. 28, 1941, under trigeminal block anesthesia showed that the lesion was larger than it had first appeared, was pedunculated and stony hard. The tumor, with a wide margin of normal tissue, was removed by block dissection.

The specimen consisted of a mass of tissue measuring 4.5 by 3.5 by 2.5 cm. and was necrotic on one surface where it showed evidence of hemorrhage. On cut section tissue was firm and gray. A diagnosis of myoblastoma was made on microscopic section.

Nov. 15, 1941, a right supra-omohyoid neck dissection was done. The specimen consisted of a mass of fibrofatty tissue measuring 5.0 by 4.5 by 3.5 cm. On section one enlarged, homogeneous, cellular gray lymph node adjacent to a piece of salivary gland was found. The microscopic diagnosis was myoblastoma metastatic to one lymph node (Fig. 6).

Dec. 2, 1941, a recurrence of tumor 1 cm. in diameter was noted at the operative site. Biopsy showed recurrent myoblastoma. The patient was advised to have another excision. He did not appear again until April, 1942, at which time he was admitted to the Massachusetts General Hospital. He had no therapy in

the interim and there was a large, partly fluctuant metastatic mass extending from the right mandible to the clavicle. There was no regression following 2,100 r of deep x-ray therapy, and it was decided that the disease was too advanced to warrant further therapy. April 25, 1942, roentgenograms of the chest showed metastases to the hilar lymph nodes. The patient was discharged for terminal care and word was received that he died Aug. 3, 1942.

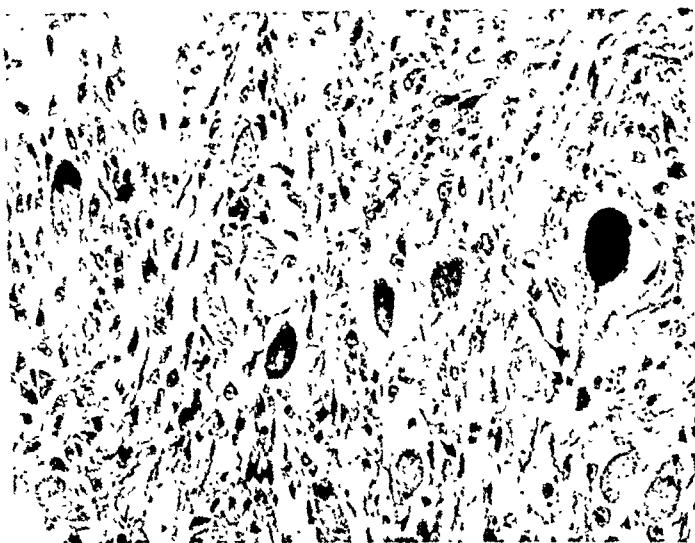


Fig. 6.—Myoblastoma, type 3 (Case 7). Note invasion of striated muscle. Phosphotungstic acid hematoxylin stain ( $\times 310$ ).

CASE 8.—W. G., a man 65 years of age, entered the Huntington Hospital complaining of a sore right chest. Six weeks previously, he had struck his right elbow severely; four and one-half weeks previously a swelling appeared in the right chest, which was poulticed for two weeks and then lanced with the escape of a considerable amount of "pus." On entry the patient showed a raised lobulated mass, ulcerated and necrotic, over the right pectoral region. This mass measured 20 by 12 by 6 cm. The peripheral nodules were moderately firm and made up of dull white tissue, whereas externally the tumor mass was dull grayish purple and necrotic. The patient died soon after entry. An autopsy showed that the tumor infiltrated and replaced a large portion of the pectoral muscle and invaded the costochondral junctions of the third and fourth ribs. The parietal pleura was not penetrated; no evidence of metastases was found. Microscopically, the tumor showed many tumor giant cells and was classified as a myoblastoma, Abrikossoff type 3.

CASE 9.—Little information is available in this case. The tumor was sent to the Warren Museum of the Harvard Medical School by the late Dr. D. F. Jones in 1928 and was exhibited as a gross specimen of sarcoma. Through the courtesy of the curator, Dr. M. M. Canavan, we were able to study this tumor, which proved to be a myoblastoma, type 2. It presented itself as a spherical gray mass, 9 cm. in diameter, embedded in the gluteal muscles. While well demarcated, it was not encapsulated. Owing to the fixation, its consistency could not be determined, but apparently was about that of the muscle. The cut surface was fairly uniform, but indefinitely fibrillar.

CASE 10.—H. H. This case is represented only by a slide found in the files of the Massachusetts State Tumor Diagnosis Service of a specimen submitted in

1925. No clinical information is available, other than that the tumor occurred in the left thigh of a man 81 years of age. The slide, diagnosed in 1925 as fibrosarcoma, shows a myoblastoma, type 3.

#### ANALYSIS OF CASES

The following analysis is based on the 44 cases collected by Klemperer,<sup>32</sup> 104 additional cases collected from the literature, regarded as meeting our criteria and summarized in Table I, and 10 cases, the tissues from which were studied in our laboratories (Table II).

*Age.*—The age distribution is not significant, as can be seen from Table I. One congenital tumor was found.

*Duration.*—Since most of the tumors are small when first noted, accurate data as to duration are almost impossible to obtain. However, of 50 cases with information regarding duration, 31 per cent of the benign lesions had been noticed for six months or less, as against 75 per cent of the malignant lesions (Table III).

*Sex.*—No significant variation in sex distribution was noted among the group.

*Topography.*—Data as to the location of the tumors are available in 158 cases (Table IV). Eighty-nine cases occurred in the upper digestive and respiratory tracts, which verifies the previously reported predisposition to occur in these regions. This predisposition may be on an embryologic basis, because these organs develop from the primitive oropharyngeal cavity and its surrounding branchial structures where embryologic malformations frequently occur. Fifty-nine cases or over one-third of the reported cases were in the tongue. These lesions in the tongue are usually, although not always, benign.

#### DIAGNOSTIC CRITERIA

*Gross Appearance:* While there is no characteristic gross appearance of myoblastoma, and the diagnosis must be made on the microscopic findings, the tumor is usually discrete, rounded, or nodular. When in relation to a mucous membrane it tends to be polypoid, but lacks the lobulation and clubbed pedicles of a polypoid rhabdomyoma. Descriptive facts were mentioned in 29 cases and are quite varied.

The following excerpts from descriptions of tumors in various locations serve as examples of the varied gross picture presented:

Bronchus—pinkish gray; broad based and pedunculated

Orbit—walnut sized, attached to bone

Bladder—mushroom shape, irregular ulcerated surface

Bladder—pedunculated base; anterior wall covered with sessile papillomas

Spinal cord—cut like a fibroma

Thoracic wall—stony hard, encapsulated, firm, grayish with overlying skin red

TABLE I  
REPORTED CASES OF MYOBLASTOMA

AUTHOR	AGE (YR.)	SEX	DURA- TION	LOCATION	SIZE AND SHAPE	MICROSCOPY	GROSS	TREAT- MENT	REMARKS
Muller <sup>43</sup>	--	--	--	Leg mus- cles at site of old un- united fracture	----	Typical, no striations	----	Amputa- tion	Appearance and clinical behavior caused author to classify it as malignant myo- blastoma
Cappell and Mont- gomery <sup>10</sup> Case 3	61	M	9 days	Bladder	2.5 x 2 cm. mushroom shaped	Neoplastic cells invading wall of bladder	Solid mushroom shaped; irregu- lar, ulcerated surface	Excision, death on table	Died under anesthetic, no autopsy
Case 4	27	F	--	Bladder	Nutmeg	Typical	Pedunculated, base and ant. bladder wall covered with sessile papil- lomas	Excision and elec- trocoagu- lation	No recurrence 6 yr.
Case 5	52	M	3 yr.	Spermatic cord	6 x 4.5 cm. ovoid	Not typical due to curious hyaline stroma	Cut like a fibroma, in cord substance not attached to testicle	Excision	Injury (fall), "The patient made an un- eventful recovery"
Case 6	60	M	2 yr.	Tongue (?) runula	4 cm. in diameter	Malignant myo- blastoma. No striations	1 cm. base, cleft near growth with ulceration in cleft	Diathermy, radium 14,620 mg. hr. in 6 mo.	Recurrent after ex- cision: recurrence measured 1.5 x 1.0 x 1.3 cm., ovoid; radium had no ef- fect on growth. Cervical glands en- larged but no biopsy; patient died sometime later— cause thought to be recurrence and sepsis

TABLE I—CONT'D

AUTHOR	AGE (YR.)	SEX	DURATION	LOCATION	SIZE AND SHAPE	MICROSCOPY	GROSS	TREATMENT	REMARKS
Morpurgo <sup>11</sup> Case 1	55	F	--	Tongue	Elevated 2 mm.	Typical	Spongy nodule, submucous tumor within muscle, yellowish brown	Excision	Mucosa normal
Case 2	65	F	--	Tongue	----	Much atypism, acceptable, malignant myoblastoma; longitudinal striations	Low, raised with central crater	Excision	
Case 3	65	M	--	Upper right leg	Nut sized	Myoblastoma, sarcomatoides	In the scar, white, encapsulated	5 radium applications, excisions	Multiple recurrence
Geschelin <sup>21</sup>	40	F	--	Left vocal cord	Pen sized	Abrikosoff type 4	----	Excision via endolaryngeal approach	No recurrence 18 mo. after last operation
Roffo <sup>17</sup> Case 1	--	--	--	Tongue	----	----	----	Excision	Hyperplasia of overlying epithelium, author feels it is degenerative and not a tumor
Case 2	31	F	3 yr.	Tongue (rt. dorsum)	Almond	Typical transitional phases seen; striations present	Hard, smooth, red surface		
Glasunow <sup>21</sup>	32	M	4 mo.	Mid-tongue	1 cm. in diameter	Typical, no striations	----	Radium 7,200 and 9,600 mg. hr., partial excision plus 960 mg. hr.	Hyperplasia of overlying epithelium
Gander <sup>20</sup>	--	--	--	Tongue	----	----	----	----	----

Parcira and Nunes de Almeida <sup>16</sup> Case 1	--	--	--	Tongue	----	----	----	----
Case 2	--	--	--	Tongue	----	----	----	----
Geschickter <sup>22</sup> 3 Cases	44	F	--	Sacral subeu- taneous	----	Typical	----	Excision, radiation
								Groins dissected; re- currence in groins 5½ yr. after ex- cision; radium im- plantation; Patient planted. Patient well 20 mo.
	--	--	--	Sacral subeu- taneous	----	----	----	----
	--	--	--	Sacral subeu- taneous	----	----	----	----
Geschickter <sup>22</sup> 1 Case	7	F	--	Skin of ear	6 x 4 x 3 cm.	Striations present	----	----
5 Cases	--	--	--	Muscles of ex- tremities	----	----	----	----
2 Cases	--	--	--	Breast	----	----	----	----
1 Case	--	--	--	Tongue	----	----	----	----
1 Case	--	--	--	Vagina	----	----	----	----
1 Case	--	--	--	Oral cavity	----	----	----	----
Gray and Gruenfeld <sup>24</sup> Case 1	30	F	3 mo.	Anterior tongue	Hazelnut	Typical	Dome-shaped protrusion on dorsum, em- bedded in mus- cle, yellowish, firm and elastic	Excision
								Intact overlying mu- cosa; no recurrence 4 yr.
Case 2	35	M	6 mo.	Left edge of tongue	6 mm. in diameter	Typical	Located sub- mucosally	Excised with small margin
								History of trauma (biting); intact grayish overlying mucosa; no recur- rence 6 yr.



TABLE 1—CONT'D

AUTHOR	AGE (YR.)	SEX	DURA- TION	LOCATION	SIZE AND SHAPE	MICROSCOPY	GROSS	TREAT- MENT	REMARKS
Case 3	55	F	--	Left chest below mammary fold	15 mm. in diameter	Typical; no transitions, no striations	Overlying skin red, encapsu- lated, firm, grayish	Excised	---
Case 4	30	F	1½ yr.	Tongue	Pea	Typical	Well demarcated, yellowish, no capsule		Tender, intact over- lying mucosa, no re- currence 3 yr.
Case 5	--	F	--	Breast	10 cm. in diameter	Typical	Grayish, firm, encapsulated	Excision in pieces	Overlying epidemoid carcinoma of the mucous membrane
Bobbio <sup>6</sup>	33	M	--	Left vocal cord	----	Typical	----	Excision	
Lattes <sup>17</sup>	49	M	1 yr.	Tongue	Small circum- scribed	Typical			
Eickhoff <sup>18</sup>	25	M	--	Tongue	Cherry	Has cross striation (?) atypical rhabdomyoma	Firm, irregular, grayish white	Excision	Epidemoid carcinoma of overlying mucous membrane
Grayzel and Friedman <sup>25</sup>	45	F	6 mo.	Thoracic wall	Globular 2.7 × 2.5 × 1.5 cm.	Typical, parallel rows of gran- ules suggesting cross striations; transitional stages seen	Stony hard	Excision	No recurrence Dec., 1939, to April, 1941
Frenekner <sup>19</sup> Case 1	25	M	--	Introitus of larynx	Lobular 3.5 × 7.5 cm.	Not typical, all cells had both longitudinal and cross stria- tions; resembles Abrikossoff's	Egg shaped and lobular but sur- face grayish red with hem- ped-sized yel- low spots	Excision, blunt dis- section	No recurrence 2½ yr., tumor appeared to infiltrate clini- cally and micro- scopically at its base

Case 6

Case 2	28	F	1 yr.	Trachea	Hazelnut 2.7 x 2 cm	Typical, no striations; pie cously diag- nosed as a rhabdomyoma	Encapsulated, broad base, sharply defined; cut surface grayish red	Trans- tracheal submu- cosal enuclea- tion	No recurrence 3 yr.
Case 3	41	M	3 yr.	Lower lip	10 x 10 x 13 mm. in situ	Typical	Overlying mucosa bluish white, partly encapsulated	Excision	Palpable pea-sized submandibular gland
Case 4	22	F	3 1/2 yr.	Tongue (lt. edge)	Pea sized	Typical	Considered to be a fibroma	Excision	Slight infiltration of tongue musculature
Case 5	48	M	1 mo.	Tip of tongue	Firm pea sized in center of a red spot	Typical	Hard and clearly defined	Excision	----
von Behr <sup>14</sup>	49	F	years	Lacrimal sac	Large pea grossly, micro- scopically 4 mm.	Typical, longi- tudinal but no cross striations	Pea sized tumor with superim- posed inflamma- tion and sup- puration	Excision	----
Kramer <sup>14</sup>	15	F	14 wk.	Ht. lower lobe bronchus, posterior mesial aspect	Completely occluded rt. lower lobe bronchus	Typical	Pinkish gray, broad based, pedunculated	Broncho- copy and punch biopsy excision in 2 stages, diathermy coagula- tion	Symptom-free with neg. x-ray 5 mo. after first broncho- copy; accompanied by lung support- tion and atelectasis
Leroux and Delarue <sup>15</sup> Case 1	37	M	--	Tongue	Small	Typical; appar- ent transition between granu- lar and muscle cells	----	----	Overlying squamous epithelium

TABLE I—CONT'D

AUTHOR	AGE (YR)	SEX	DURA MOR	LOCATION	SIZE AND SHAPE	MICROSCOPY	GROSS	TRT <sup>1</sup> - MNT	RE MARKS
CASE 2	45	M	--	Tongue	Small	Typical, apparent transition between granular and muscle cells	----	----	Apparent transitions between granular and epitheloma cells even more convincing than between granular and muscle cells in both these tumors, overlying squamous epitheloma
Case 3	At birth	--	--	Upper gum	----	----	----	----	Thin overlying epithelium; apparent continuity between its cells and the granular cells
Sjoegren <sup>10</sup>	8	M	5 mo	Orbit	Walnut	Varied, myoblastoma with sarcomatous like areas; in histologic evidence longitudinal and cross striations	Walnut sized nodular, adherent to pericosteum, recurrent	Radium, later excision, recurrence, eventual enucleation of orbit	Tumor enlarged, patient gradually failed and died, no post mortem; cervical adenopathy, clinically not significant
Dustin <sup>1</sup>	30	M	--	Tongue	----	Typical, longitudinal and cross striations	----	----	----
Kernan and Crocower <sup>29</sup>	21	F	3 mo.	Left vocal cord	Posterior $\frac{2}{3}$ of cord	Typical	Triable	Excision	Hyperplastic overlying epithelium simulating squamous cell epitheloma; one recurrence, no recurrence 8 mo. later

Imperator <sup>127</sup>	23	M	10 mo.	Left vocal cord	Size of two peas, lobular sessile	Typical	Papillary, firm; pale yellow, homogeneous	Excision	Hyperplasia of overlying epithelium, mucous gland metaplasia columnar to squamous; no recurrence, 4 mo.
Martinez <sup>11</sup>	50	F	18 yr.	Tongue	Oval 2 × 1.5 cm.	Typical, longitudinal and cross striations	Raised with central white plaque	Excision	No recurrence 8 mo., hyperplasia of overlying epithelium
Cioni <sup>11</sup>	48	M	--	Left adrenal	Globular	Atypical	"Meaty," grayish white, mottled	--	Metastases to pleurae, patient expired
Tam and Kowies <sup>12</sup>	39	F	3 yr.	Rt. labium majus	2.5 cm. in diameter	Typical	Firm and elastic, on cut section appears like dense connective tissue	Excision	No recurrence 1 yr.
Lino <sup>39</sup>	24	F	--	Tongue	----	Granular cells pleomorphic; many granular cells and some striations	----	Excision	----
Ducuing, Ducuing and Bassall <sup>16</sup> Case 1	34	M	20 mo.	Tongue	Small pea, round	Epidermoid carcinoma of mucosa; granular cell, myoblastoma below	Hard, yellowish	Excision	Patient well 4½ yr.
Case 2	52	M	2 mo.	Tongue	Small pea	Granular cell myoblast, epithelial hyperplasia	Whitish	Excision	Patient well 1 yr.
Case 3	22	M	2 mo.	Tongue	½ pea	Epithelioma granular cell	Hard	Excision and electrocoagulation	Patient well 1 yr.
Case 4	44	M	6 mo.	Tongue	Pea	Granular cell	Hard	Excision	Patient well 6 mo.

TABLE I—CONT'D

AUTHOR	AGE (YR.)	SEX	DURATION	LOCATION	SIZE AND SHAPE	MICROSCOPY	GROSS	TREATMENT	REMARKS
Seiffert <sup>19</sup>	17	F	--	Tongue	½ pea	Granular cell	---	Excision	Patient well 1 yr., marked epithelial hyperplasia
Cyatte and Ducoiron <sup>22</sup>	35	F	2 yr.	Tongue	2 × 1 cm.	Granular cell and some fibers with striations	Hard	Electro-coagulation	
Bang <sup>5</sup>	63	--	--	Tongue	----	Granular cell	Hard	---	
Bernier, Mann, and Ash <sup>7</sup>	2 wk. F	F	--	Mandible and maxilla	----	Granular cell	Hard	---	Patient well 5 yr.
Case 1	--	F	--	Tongue	Two pieces: 1.5 × 1.0 × 1.0 cm., 1.3 × 0.5 × 0.5 cm.	Typical	Grayish white with areas of hemorrhage	Excision	Lesion operated upon four times previous to last excision
Case 2	77	F	8 yr.	Rt. middle ear or external auditory canal	1.5 × 0.7 × 0.6 cm.	Typical	Blotted, polypoid	Excision	---
Additional Cases	--	--	--	Tongue	----	----	----	---	---
5	--	--	--	Lip	----	----	----	---	---
1	--	--	--	Lip	----	----	----	---	---

2	--	--	--	Alveolar process of maxilla or mandible	----	----	----	----
1	--	--	--	Floor of mouth	----	----	----	----
1	--	--	--	Trachea and bronchi	----	----	----	----
3	--	--	--	Skin	----	----	----	----
10	--	--	--	Subcutis	----	----	----	----
1	--	--	--	Muscles of extremities	----	----	----	----
2	--	--	--	Breast	----	----	----	----
Thoma <sup>53</sup>	30	F	1½ yr.	Tongue (anterior third)	1.4 × 2.3 × 1.0 cm.	Typical	----	----
Syathmóry <sup>51</sup>	--	--	--	Vulva	----	----	----	Accepted in literature; original article not available to us
Kratochvil <sup>55</sup>	--	--	--	Alveolar ridge	----	----	----	Accepted in literature; original article not available to us
Lol <sup>40</sup>	--	--	--	Lower lip	----	----	----	Accepted in literature as a malignant tumor; original article not available to us
von Albertini <sup>53</sup>	--	--	--	Tongue	----	----	----	Original article not available to us

TABLE II  
NEW CASES

OUR CASES	AGE	SEX	DURATION (MO.)	LOCATION	SIZE AND SHAPE	GROSS	ABRIKOS-SOFF TYPE	TREATMENT	REMARKS
Case 1	35	F	2½	Left deltoid	4 cm. in diameter, fusiform	On section, firm, multicolored, poorly retracted, poorly demarcated, infiltrating	Type 2	Excision	Later developed swelling over right humerus and over right ulna. These regressed on x-ray therapy. Patient had tetral poisoning. Proved metastases to lungs, etc. Patient expired
Case 2	64	M	24	Left side of tip of tongue	7 mm. in diameter	Elevated 1 mm.; firm, whitish gray, granular	Type 2	Partial glossectomy	Mental case—no history; hyperkeratosis of overlying mucous membrane, no recurrence 16 mo.
Case 3	17	F		Left buttock	Size and shape of small hen's egg	Egg-sized mass; slightly movable	Type 2	Excision, x-radiation	Tumor occurred at site of trauma, no recurrence 1 yr.
Case 4	81	M	12+	Lower left thigh	2.5 cm. in diameter, ovoid	Adherent to fascia, ovoid, grayish white periphery, soft degenerated center	Type 2	Excision	One recurrence after primary excision; no recurrence one year after second excision
Case 5	24	M	24	Palm left hand	Pea size growing to olive size	First specimen not seen; second specimen indurated scar 7 × 6 × 3 cm.	Type 2	1. Excision 2. Partial amputation of hand 3. Amputation of forearm and axillary dissection	Large axillary lymph nodes, but all 52 nodes negative for tumor; no recurrence 6 mo. after excision

Case 6	52	F	1½	Midnight thigh	10 cm. + in diameter	10 cm. in diameter; infiltrating 4 cm. in diameter fungating mass	Type 3	X-radiation	Local lesion disappeared after x-ray; died with pulmonary metastases
Case 7	71	M	1+	Buccal mucous membrane	4.5 × 3.5 × 2.5 cm.	Firm and gray, one necrotic surface	Type 3	Excision, x-radiation	Died with extensive cervical and pulmonary metastases
Case 8	66	M	1½+	Right peritonal region	20 × 16 × 6 cm., pedunculated	Whitish, dull tissue where not necrotic	Type 3	No treatment	Expired from sepsis secondary to the tumor
Case 9				Buttocks	9 cm. in diameter, spherical	Gray, well-delineated but not encapsulated	Type 2	Excision	Specimen in Warren museum; no history available
Case 10	81	M		Left thigh			Type 3		Slide found in tumor clinic files; no history available



and sometimes contain vacuoles. In some of the larger cell masses, granulations are present in the cytoplasm. In a few of the cells, particularly in the better differentiated tumors, these may represent precursors of the cross striations. This type of myoblastoma rarely grades almost imperceptibly into the definitely rhabdomyomatous tumor, but usually is distinctive. The tumor is sometimes separated from adjacent normal muscle fibers by a definite connective tissue capsule. Often the peripheral cells interdigitate with the adjacent normal muscle bundles.

In the malignant variant of this tumor, the granular-cell type of myoblast may be in part replaced by more variable cells, among which a moderate degree of mitotic activity is present. The larger protoplasmic masses may contain very bizarre giant nuclei, sometimes showing evidence of abnormal mitoses and abnormal increase in chromosome number.

The stroma is usually fine and scattered. The degree of vascularization is variable, but blood channels are not a prominent feature of the tumor.

#### TREATMENT

On the basis of available data 37 patients were treated by surgical excision, 3 by excision and electrocoagulation, 5 by excision and radium therapy, and 1 by electrocoagulation. Follow-up data is too incomplete to be significant. It is presented in Tables I and II. A few points deserve emphasis. One patient had a recurrence and was well eight months after re-excision. Another had recurrence and metastases from the sacrum to the groin five and one-half years after primary excision and was well twenty months after dissection and radium therapy. One patient remained well five months after bronchoscopic electrocoagulation.<sup>34</sup>

One patient with tumor of the leg had five applications of radium, dosage not specified, and excision for recurrences; the end result is unknown.<sup>43</sup> One myoblastoma of the tongue was treated by electroexcision followed by 14,620 mg. hr. over a period of six months. The patient later died.<sup>10</sup> One myoblastoma of the orbit was treated by extensive radium therapy, dosage unknown, followed by excision and later exenteration of the orbit. The patient finally died of the disease.<sup>50</sup>

We know of only 5 patients treated with radium. In one tumor of the tongue there was relief of pain but no effect on the growth. In the previously mentioned myoblastoma of the orbit, and in one of the leg, radiation had no apparent effect. In our Case 3, L. F., from the Westfield State Sanatorium, x-radiation was applied to the tumor bed after the tumor had been excised. In Case 6, the patient responded to roentgen therapy. The local tumor regressed completely, but the patient died of pulmonary metastases.

## MALIGNANCY

In searching the literature on myoblastoma for cases with evidence of malignancy, two facts are outstanding:

1. Locally invasive and histologically malignant tumors exist, although they are rare.
2. Metastasis either by blood stream or lymphatic channels is unusual.

Some myoblastomas were coincident with carcinoma. These usually developed in the upper respiratory passages and skin as a result of the abnormal proliferation of the overlying epithelium, which characterizes many myoblastomas. Data as to this feature are available in 29 cases and, of these, in 13 or 45 per cent there was abnormal proliferation and in 8 or 28 per cent there was definite epidermoid carcinoma. In the remaining 8 cases, the condition of the overlying epithelium was normal.

Leroux and Delarue,<sup>38</sup> in reporting two tumors of the tongue, thought that the apparent transitions between granular cells and epithelioma cells were even more convincing than between granular and muscle cells, but this is not the prevalent opinion.

In 10 of the cases from the literature and 4 of our own, there was either gross or microscopic evidence of local invasion or malignancy of the myoblastoma itself. Although there was regional adenopathy in 7 cases, in only 3 (Geschickter's and our Cases 1 and 7) were *metastases to lymph nodes proved by biopsy*.

The following are brief abstracts of those reported cases we consider as showing malignant characteristics:

Myenburg<sup>45</sup> reports a case of myoblastic sarcoma of the tongue in a 57-year-old man which presumably recurred after excision, was locally malignant, and resulted in hemorrhage and death.

The tumors in two of Morpurgo's<sup>43</sup> cases showed malignant characteristics, and study of his photomicrographs gives convincing evidence. The first was a tumor of the dorsum of the tongue in a 65-year-old woman and was diagnosed clinically as a carcinoma. It was described as a villous excrescence, later progressing to a raised lesion with a central undermining crater. Dental trauma was thought to be a factor. No metastatic nodes were demonstrated. The tumor was excised and the specimen consisted of nearly all of the left dorsum of the tongue. There were many mitotic figures and the tumor was invasive. No follow-up is given.

Morpurgo's second case was that of a 65-year-old man who had a nodule excised from the upper portion of the right leg following five applications of radium. The tumor recurred twice after excision. A microscopic diagnosis of myoblastoma sarcomatoides was made on the basis of its being more primitive and complex, simulating spindle-cell sarcoma. This case would apparently fall under type 3 in Abrikos-

soff's<sup>1</sup> classification. There appears to be no necessity for the term myoblastoma sarcomatoides.

Cappell and Montgomery<sup>10</sup> quote briefly a case recorded by Muller,<sup>44</sup> in 1917, as a rhabdomyoma, which they feel should be classified as a malignant myoblastoma. This was a tumor originating in the skeletal muscles of the leg at the site of an ununited fracture. The tumor failed to exhibit striations, but its staining and morphology indicated its origin from striated muscle. The subsequent history after amputation is not recorded but the appearances and clinical behavior suggest that the growth was malignant.

The same authors<sup>10</sup> present two of their own cases. The first was a myoblastoma of the tongue in a 60-year-old man, diagnosed clinically as a ranula and excised. It recurred a year later together with cervical adenopathy. It was excised and recurred again two years later and grew to involve the right tonsil and anterior pillar. It was treated by diathermy and radium to the extent of 14.620 mg. hr. The radium diminished the pain but had no effect on the growth. The patient eventually died and, although there was no autopsy, it was thought that death was due to recurrence in the mouth and nodes followed by sepsis. The photomicrographs are acceptable as myoblastoma. Metastasis was not proved pathologically.

Their second malignant case was a myoblastoma in the bladder of a 61-year-old man, with hematuria for nine days. Cystoscopic examination and later cystotomy revealed a mushroom-shaped stalk 2 cm. long and 2.5 cm. in diameter, about one and one-half to two inches above the ureteric ridge. Unfortunately, the patient died under anesthesia. Microscopic examination of the removed specimen showed invasion of the bladder wall, so that, had the patient lived, there would have been a recurrence. The cytology in the accompanying photomicrographs is consistent with the diagnosis of myoblastoma.

Sjogren<sup>50</sup> reports a case of malignant myoblastoma of the orbit in an 8-year-old boy. A tumor was excised from under the left orbital ridge and at first was diagnosed as xanthosarcoma. It recurred postoperatively, and he developed cervical adenopathy, which was thought not to be significant. A course of x-ray therapy had no effect and the tumor was again excised and found to involve the superior oblique muscle and supraorbital nerve. It again recurred and finally an exenteration of the orbit was done, but there was further recurrence involving the bony structures of the orbit, and the patient finally died with a large protruding, painful, fluctuant tumor. The microscopic pictures of the later recurrence were compatible with myoblastoma. In certain fields there was a sarcomatous appearance and there were a few striated cells present.

Geschiekter<sup>22</sup> reports a case of proved metastatic myoblastoma in a woman aged 44 years, with metastases to both groins from the region of the sacrum. Five and one-half years after excision of the primary

lesion there was an ulcer at the site of the original growth and masses in both groins, larger on the left. The growth on the right was excised and found to be well encapsulated. On the left, the growth infiltrated the surrounding tissue and was adherent to the femoral artery. Some tumor tissue was left behind on the artery and four 1 mc. radon seeds were implanted. The patient was reported well twenty months later. Through the courtesy of Geschickter and Horsley, we have been able to examine the slides of the lesion, which appear typical.

Cioni<sup>11</sup> reports a case of a malignant myoblastoma of the adrenal gland with metastases to the pleura in a 48-year-old man, which appears acceptable as an Abrikossoff type 4 tumor.

Loi<sup>10</sup> reports a case of a malignant myoblastoma of the lower lip. The description is not available to us, but other writers have recorded it as malignant.

Our own cases of malignant myoblastoma are reported as Cases 1, 6, 7, 8, and 10. That the more histologically variable types of myoblastoma may metastasize has been clearly proved. The commoner sites for these metastases are the regional lymph nodes and the lungs.

In most of the malignant cases, it was noted that there was: (1) atypism of cells, (2) excessive mitotic figures, (3) spindle-shaped cells, and (4) local invasion.

Age had no clear influence on the occurrence of malignant myoblastic tumors. The patients ranged from 8 to 81 years of age, although 9 of 13 were over 50 years of age.

#### CONCLUSIONS

1. Myoblastoma is a tumor entity becoming more generally recognized. It is derived from embryonic myoblasts and may be distinguished from the rhabdomyoma group.

2. We have reviewed the clinical data and microscopic findings of 104 cases collected from the literature, exclusive of those reported by Klemperer, and present 10 new cases.

3. Fifty-six per cent of these occur in the upper respiratory and digestive tracts.

4. Fifty-nine cases occurred in the tongue and of these, 3 or 5 per cent were malignant.

5. Eleven per cent of the total cases were malignant and of these, only 3 showed proved metastasis.

6. Whenever a myoblastoma is reported to have (1) atypism of cells, (2) excess mitotic figures, (3) spindle-cell or sarcomatous pattern, or (4) local invasion, it should be treated surgically as a malignant tumor until more is known of the nature of these growths, especially if the patient is over 50 years of age.

7. The degree of radiosensitivity and frequency of metastasis are as yet unknown. Both appear to be low.

8. Tumors under mucous membrane or skin have a marked tendency to be associated with hyperplasia and epidermoid carcinoma of the overlying epithelium.

## REFERENCES

1. Abrikossoff, A. J.: Über Myome, ausgehend von der quergestreiften willkürlichen Muskulature, *Virchows Arch. f. path. Anat.* 260: 215, 1926.
2. Abrikossoff, A. J.: Weitere Untersuchungen über Myoblastenmyome, *Virchows Arch. f. path. Anat.* 280: 723, 1931.
3. von Albertini, A.: Zur Frage der Myoblastenmyome der Zunge, Schweiz. Ztschr. f. allg. Path. u. Bakt. 1: 431, 1938.
4. von Bahr, G.: Myoblastic Myoma of Lacrimal Sac, *Acta ophth.* 16: 109, 1938.
5. Bang, F.: Et tilfaelde af rhabdomyoma granulocellulare (myoblastmyom) i tungen, *Ugesk. f. læger* 99: 710, 1937.
6. Berner, O.: New Muscle Tumor. Case of Myoblastio Myoma, *Norsk mag. f. lægevidensk.* 92: 706, 1931.
7. Bernier, J. L., Mann, J. B., and Ash, J. E.: Myoblastoma, Maxilla and Mandible, *Atlas of Dental and Oral Pathology*, ed. 2, Chicago, 1942, Am. Dent. Assoc., p. 102.
8. Bernier, J. L., Mann, J. B., and Ash, J. E.: Myeloblastoma, Tongue, *Atlas of Dental and Oral Pathology*, ed. 2, Chicago, 1942, Am. Dent. Assoc., p. 103.
9. Bobbio, A.: Mioblastoma ad elementi granulosi (mioblastomioma di Abrikossoff) della laringe, *Arch. per le sc. med.* 61: 383, 1936.
10. Cappell, D. F., and Montgomery, G. L.: On Rhabdomyoma and Myoblastoma, *J. Path. & Bact.* 44: 517, 1937.
11. Cioni, C.: Considerazioni sui tumori di tessuto muscolare (mioblastoma maligno della ghiandola surrenale con metastasi pleuriche), *Arch. ital. di anat. e istol. pat.* 7: 484, 1936.
12. Civatte, A., and Ducourtioux, M.: Un nouveau cas de rhabdomyome de la langue, *Bull. Soc. franç. de dermat. et syph.* 46: 1458, 1939.
13. Derman, G. L., and Golbert, Z. W.: Über unreife, aus der quergestreiften Muskulatur hervorgehende Myome, *Virchows Arch. f. path. Anat.* 282: 172, 1931.
14. Dewey, K. W.: Rhabdomyoma of the Tongue, *Arch. Path.* 3: 645, 1927.
15. Diss, A.: Le rhabdomyome granulocellulaire de la langue, *Ann. d'anat. path.* 7: 1071, 1930.
16. Ducuing, J., Ducuing, L., and Bassal: Le rhabdomyome granulocellulaire de la langue, *Presse méd.* 46: 1018, 1938.
17. Dustin, A. P.: Myoblastic Myoma of Tongue, *Acta, Union internat. contre cancer* 4: 683, 1939.
18. Eickhoff, H.: Myoblastenmyom und Carcinom, *Virchows Arch. f. path. Anat.* 304: 432, 1939.
19. Freckner, P.: Occurrence of So-called Myoblastomas in the Mouth and Upper Air Passages, 5 Cases, *Acta oto-laryng.* 26: 689, 1938.
20. Gander, G.: Du rhabdomyome granulocellulaire de la langue, *Bull. Assoc. franç. p. l'étude du cancer* 24: 56, 1935.
21. Geschelin, A. I.: Fall von Myoblastomyom des Kehlkopfs, *Acta oto-laryng.* 21: 66, 1934.
22. Geschickter, C. F.: Tumors of Muscle, *Am. J. Cancer* 22: 378, 1934.
23. Glasunow, M.: Über unreife, begrenzt und destruierend, wachsende Rhabdomyoblastome, *Frankfurt. Ztschr. f. Path.* 45: 328, 1933.
24. Gray, S. H., and Gruenfeld, G. I.: Myoblastoma, *Am. J. Cancer* 30: 699, 1937.
25. Grayzel, D. M., and Friedman, H. H.: Myoblastoma of the Thoracic Wall, *Arch. Path.* 31: 512, 1941.
26. Horn, R. C., and Stout, A. P.: Granular Cell Myoblastoma, *Surg., Gynec. & Obst.* 76: 315, 1943.
27. Imperatori, C. J.: Rhabdomyoma of Larynx, *Laryngoscope* 43: 945, 1933.
28. Jaulin, and Grandclaude, C.: Un cas de rhabdomyome granuleux de la langue, *Bull. Assoc. franç. p. l'étude du cancer* 18: 395, 1929.
29. Kernan, J. D., and Crocovaner, A. J.: Rhabdomyoma of Vocal Cord, *Laryngoscope* 45: 891, 1935.
30. Keynes, G.: Rhabdomyoma of the Tongue, *Brit. J. Surg.* 13: 570, 1926.
31. Kleinfeld, L.: Myoblastoma of the Larynx, *Arch. Otolaryng.* 19: 551, 1934.
32. Klemperer, P.: Myoblastoma of Striated Muscle, *Am. J. Cancer* 20: 324, 1934.

33. Klinge, F.: Über die sogenannten unreifen, nicht quergestreiften Myoblastenmyome, Verhandl. d. deutsch. path. Gesellsch. 23: 376, 1928.
34. Kramer, R.: Myoblastoma of Bronchus, Ann. Otol., Rhin. & Laryng. 48: 1083, 1939.
35. Kratochvíl, K.: Beitrag zum Vorkommen der Myoblastengeschwülste, Arch. f. klin. Chir. 201: 83, 1941.
36. Lascano-González, J. M.: Observaciones de miomas mioblasticos (Abrikossoff), Rev. Asoc. méd. argent. 55: 300, 1941.
37. Lattes, R.: Mioblastoma ad elementi granulosi della lingua, Arch. per le sc. med. 61: 590, 1936.
38. Leroux, R., and Delarue, J.: Sur trois cas de tumeurs a cellules granuleuses de la coirte buccale, Bull. Assoc. frang. p. l'étude du cancer 28: 427, 1939.
39. Lino, G.: Contributo allo studio dei tumori rari della lingua e della istogenesi del rhabdomioma, Tumori 14: 373, 1928.
40. Loi, L.: Sudi un mioblastoma maligno del labbro inferiore, Arch. ital. di med. sper. 3: 343, 1938.
41. Martinez, E. M.: Sobre una observación de rabdoinoma granulocelular (Diss), Arch. de med. int. 1: 281, 1935.
42. Meyer, R.: Myoblastentumoren (Myoblastenmyome, Abrikossoff), Virchows Arch. f. path. Anat. 287: 55, 1932.
43. Morpurgo, B.: Mioblastomi, Arch. per le sc. med. 59: 229, 1935.
44. Muller: 1917, Quoted by Cappell and Montgomery.<sup>10</sup>
45. Myenburgh, H.: In Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, 1929, Springer, vol. 9, pt. 1, p. 468.
46. Parreira, H., and Nunes de Almeida, J.: Dois casos de rabdomioma da lingua, Arq. d pat. 6: 582, 1934.
47. Roffo, A. H.: Knotige Zungenmyolyse, Ztschr. f. Krebsforsch. 39: 464, 1933.
48. Schirmer, R.: Über ein Myoblastenmyom zusammen mit Canceroid der Zunge, Beitr. z. path. Anat. u. z. allg. Path. 89: 613, 1932.
49. Seiffert, A.: Myoblastenmyom der Zunge, Ztschr. f. Laryng., Rhin. Otol. 26: 4, 1935.
50. Sjogren, H.: Myoblastoma malignum orbitae, Arch. f. Ophth. 134: 333, 1935.
51. Syathmóry, Z.: Perineal Myoblastoma, Magyar orvosi arch. 38: 260, 1937 (cited).
52. Tamis, A. B., and Kowles, J. J.: Myoblastoma of Labium Majus, Am. J. Obst. & Gynec. 42: 543, 1941.
53. Thoma, K. H.: Rhabdomyoma of Tongue, Am. J. Orthodontics (Oral Surg. Sect.) 27: 235, 1941.
54. Wolbach, S. B.: Centrioles and Histogenesis of Myofibril in Tumors of Striated Muscle Origin, Anat. Rec. 37: 255, 1928.
55. Wolbach, S. B.: Malignant Rhabdomyoma of Skeletal Muscle, Arch. Path. 5: 775, 1928.

# MALIGNANT PAPILLARY CYSTADENOMA OF SWEAT GLANDS WITH METASTASES TO THE REGIONAL LYMPH NODES

ROBERT C. HORN, JR., M.D., PHILADELPHIA, PA.

*(From the Laboratory of Surgical Pathology, Hospital of the University of Pennsylvania)*

ALTHOUGH sweat gland tumors have been recorded in the literature not infrequently, reports of cases of proved malignancy are rare. Most of the carcinomas of sweat glands which have been described were considered malignant on the basis of histologic invasive or anaplastic growth, metastasis being exceptional. In this communication, a sweat gland tumor of well-defined papillary structure is described which, in addition to showing invasive growth locally, metastasized to the regional lymph nodes.

Gates, Warren, and Warvi<sup>1</sup> have recently published a review of tumors of sweat glands. They collected from the literature twenty-nine cases of carcinoma which they considered to be clearly of sweat gland origin and added six of their own. Among the tumors of questionable malignancy which they excluded are the numerous reported cases of adenocarcinoma of the vulva (McDonald<sup>2</sup>), which, with the exception of Eichenberg's<sup>3</sup> tumor, have not metastasized. Metastasis occurred in only four of the thirty-five cases reviewed by Gates and associates. Hedinger<sup>4</sup> reported a sweat gland carcinoma of the scalp, which was excised together with two 1 cm. cervical lymph nodes which were the site of metastases. The tumor reported by Hufschmitt and Diss<sup>5</sup> also involved the scalp; six months after excision, it recurred with regional metastases. It was adherent to the periosteum of the skull. Moriconi<sup>6</sup> described a sweat gland cancer which arose in the axilla and metastasized to the axillary nodes. The patient was well and without evidence of disease five years after excision of the primary tumor and radical axillary dissection. Eichenberg<sup>3</sup> described a tumor occurring on the labium majus and giving rise to one small inguinal lymph node metastasis. An additional case is that recorded by Suzuki<sup>7</sup> of a medullary sweat gland carcinoma of the patellar region, which metastasized to the inguinal and femoral lymph nodes.

In addition to these cases with metastases, four of the tumors reported by Gates and co-workers and two of the tumors collected by them from the literature (Morisani,<sup>8</sup> Diss and Peterschmidt<sup>10</sup>) recurred locally fol-

lowing surgical excision. Morisani's tumor also invaded the tarsal bones, and that described by Thierfelder<sup>11</sup> invaded the frontal bone and the meninges. One of Gates' tumors invaded the auricular cartilage.

#### CASE REPORT<sup>\*</sup>

L. K. (No. 50925), a 31-year-old Hebrew man, was first admitted to the Hospital of the University of Pennsylvania, May 13, 1942, with a painless, slowly growing mass on the radial aspect of the left wrist, about 4 cm. proximal to the radial styloid. It had first been noted fifteen years before (1927), several months after an accident in which a steel sled runner had passed over the wrist without, however, producing serious injury (Fig. 1). The lesion was biopsied in 1931 and again in 1933. At this time the patient first complained of diminution in sensation over the dorsal and radial portion of the left hand. No treatment was attempted

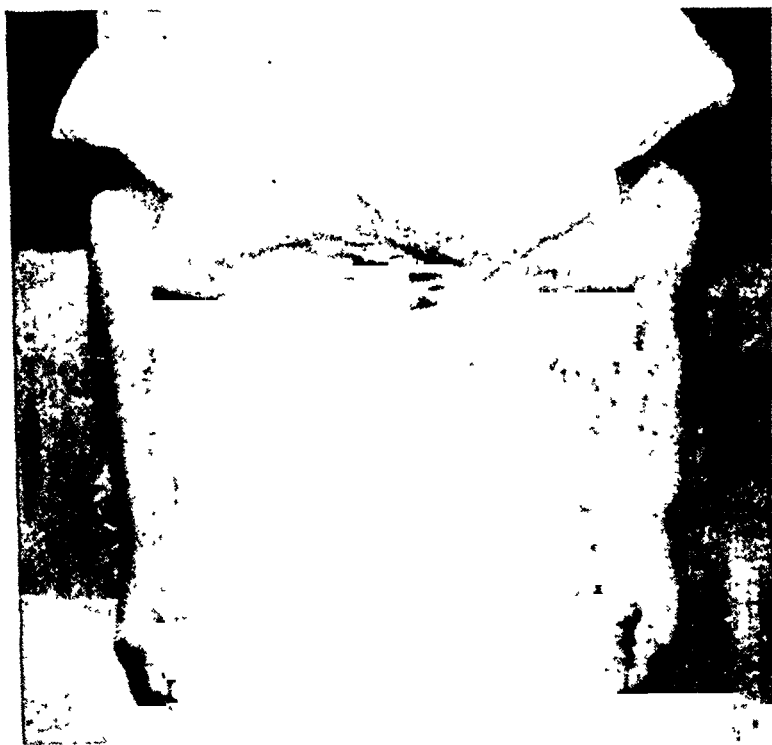


Fig. 1.—Reproduction of a snapshot of the patient at the age of 16. The tumor of the left wrist is readily visible.

until 1937, when the lesion was excised. The tumor began to recur nine months after this procedure and a second excision was done in 1940. Shortly after this, enlargement of left axillary and epitrochlear lymph nodes was noted. Another biopsy was done in May, 1941, after the tumor had again recurred locally. These surgical procedures were carried out by different surgeons in different hospitals.

The physical findings on admission to this hospital were limited to the mass on the radial side of the left forearm just proximal to the wrist, which measured 10 by 5 by 2 cm., and discrete, enlarged nodes in the left axillary and epitrochlear regions. Sensation was diminished over the dorsal and radial part of the hand

<sup>\*</sup>This case is reported with the permission of Dr. William H. Erb



and the left radial pulse was weak compared with the ulnar. X-rays of the left wrist showed a large defect in the distal portion of the volar aspect of the radius associated with a soft tissue mass (Fig. 2).

May 15, 1942, a left axillary dissection was carried out and two weeks later, several days before discharge, the lesion of the forearm was biopsied. The patient was readmitted June 21, 1942, and excision of the primary tumor was attempted the following day. An incision was made on the radial side of the forearm. Widespread invasion of the soft tissues, including the muscles, and of the radius

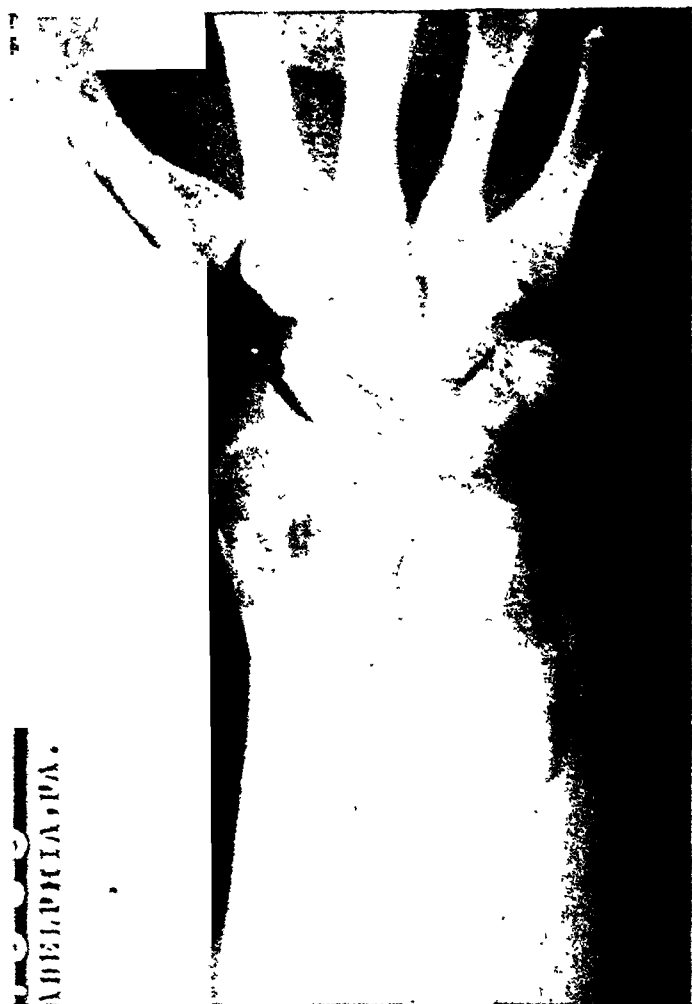


FIG. 2.—X-ray of forearm, showing destructive lesion of the distal part of the radius.

was found. Although much of the tumor was removed and the cavity in the radius was curetted, all of the tumor could not be reached through this incision and the operation was terminated. Another attempt was made to excise the local tumor, this time through an incision on the flexor surface of the forearm, July 6, 1942, but the disease was too extensive to permit complete removal. June 29, 1942, an enlarged epitrochlear lymph node was removed.\*

\*This specimen was examined by Dr. William E. Ehrlich, Chief of the Division of Pathology of the Philadelphia General Hospital, who has kindly permitted me to study the sections. The patient was discharged July 15, 1942.

Between July 22 and Aug. 21, 1942, the axilla was treated with x-ray irradiation. A total of 5950r was delivered through 15 by 20 cm. anterior and posterior fields and a direct axillary field 9 cm. in diameter. The factors were 200 kr., 15 Ma., 50 cm. skin-target distance and filters, 1 mm. Al and  $\frac{1}{2}$  mm. Cu. (200r had previously been given to the epitrochlear region).

The patient was admitted for the third time Oct. 30, 1942, for excision of two recurrent nodules in the forearm, and for the fourth time Jan. 7, 1943, for repair of an indirect inguinal hernia. X-rays taken Oct. 31, 1942, showed considerable filling in of the defect in the radius.

When the extent of this patient's disease was first realized, amputation of the arm was advised. He repeatedly refused to consider radical treatment until December, 1943, by which time the arm and hand were markedly edematous and there were extensive recurrences palpable in the scarred area on the radial aspect of the forearm (Fig. 3). On December 13, 1943, amputation was performed just distal to the deltoid insertion but above the upper limits of the edema.



Fig. 3.—Photograph of the patient one month before amputation. In addition to the tumor and scarring of the forearm, there is generalized swelling below the mid-portion of the arm.

#### PATHOLOGIC DESCRIPTION

*Gross.*—The arm, amputated 12 cm. above the elbow, was greatly swollen, large amounts of thin clear fluid escaping from the tissues on incision. A large tumor mass invaded and destroyed all the soft tissues of the dorsal part of the distal 12 cm. of the forearm, involving to a limited degree the radial aspect of the palmar surface as well. The skin overlying this mass was extensively scarred and firmly bound to the tumor tissue. The distal 4 cm. of the radius was destroyed

by the tumor, only segments of the cortical outline being discernible (Fig. 4). Proximal to the area of destruction, the bone was rough and extremely dense with a very small marrow cavity. Although surrounded on three sides by the growth, the ulna was not involved. The radiocarpal joint was invaded at one point, there being a small area of neoplastic involvement of the lunate bone and the articular cartilage.

The tumor was composed of adherent nodules varying in diameter from a few millimeters to 1.5 cm. Some of these, in general the smaller ones, were solid but soft, pale gray, and frequently gelatinous. Other nodules were larger and dark blue, proving to be thin-walled cysts containing moderately thin, bluish-red fluid. Soft, pink tissue was usually found adherent to the lining of these cysts, at times completely filling them.

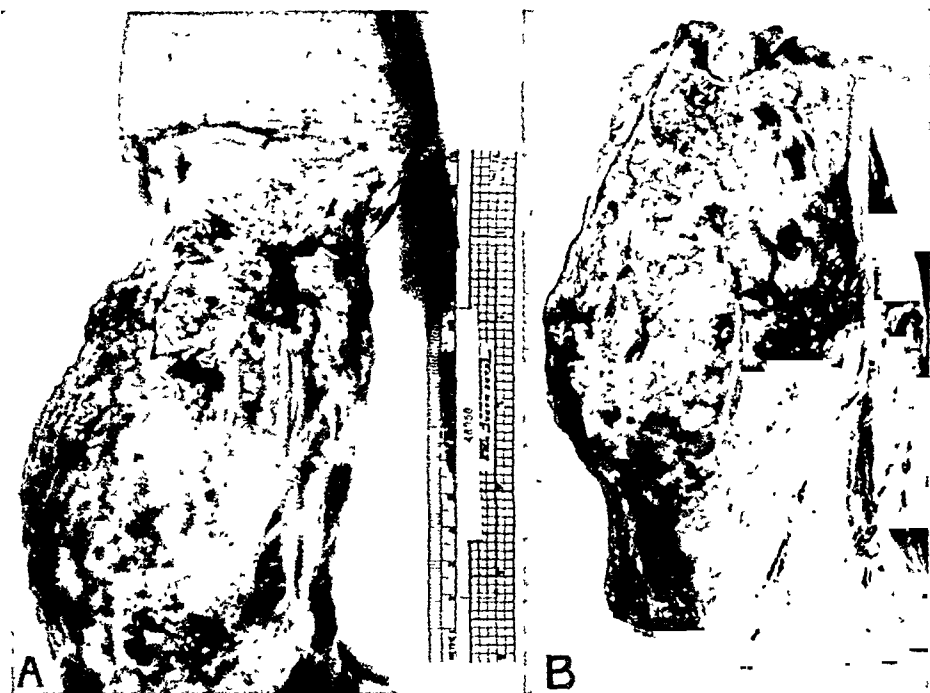


Fig. 4.—Gross appearance of the tumor. A shows the dorsal aspect of the forearm, B the cut surface. The arrow indicates the radiocarpal joint, adjacent to which a small portion of the radius is preserved.

A mass of similar tumor tissue about 3 cm. in diameter was also found in the depth of the operative scar in the epitrochlear region.

The tumor had a similar gross appearance in all of the specimens previously excised and studied in this laboratory, including the axillary lymph nodes.

*Microscopic.*—The tumor was composed of a number of cystic cavities sometimes lined by a single layer of epithelium, but more often with a papillary growth which more or less filled the lumen. The cells were generally cylindrical or cuboidal. The nuclei were ovoid and fairly uniform. Some of the cells contained droplets of material which had the staining properties of mucin. This material was abundant in the gland spaces formed in many of the more solid papillomas (Fig. 5). Fresh hemorrhage and deposits of hemosiderin were observed in the lumens and walls of many of the cysts. In general the cysts were well circumscribed, the tumor tissue being confined within them. These cysts were widely distributed throughout the soft tissues, invading especially the skeletal muscles (Fig. 6). The



\* Fig. 5.—Photomicrograph illustrating the intracystic papillary structure of the tumor (hematoxylin and eosin,  $\times 150$ ). The inset shows the glandular pattern in a higher magnification (hematoxylin and eosin,  $\times 300$ ).

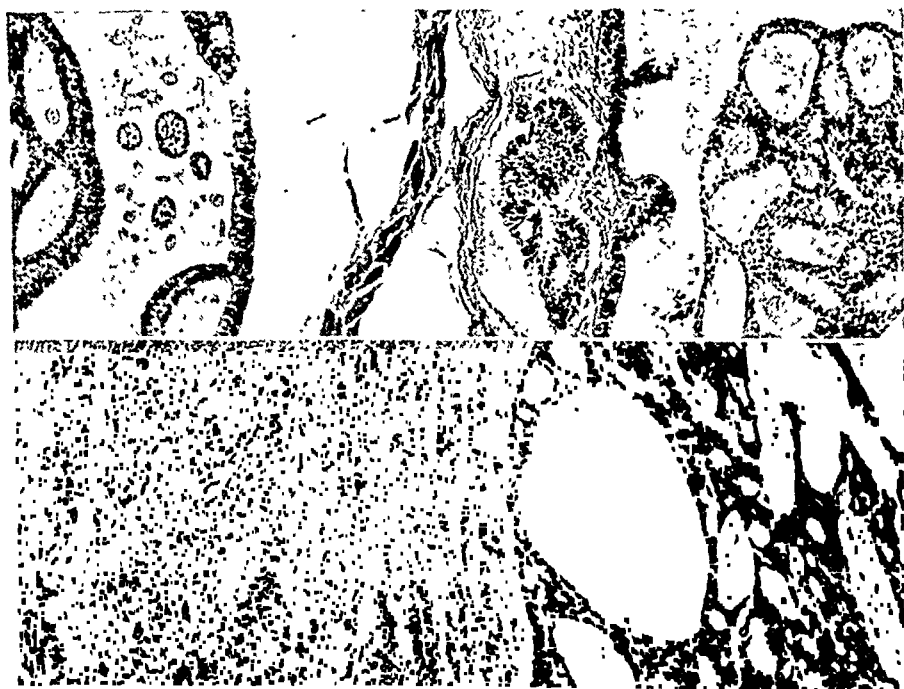


Fig. 6.—Malignant papillary cystadenoma of sweat glands invading skeletal muscle (hematoxylin and eosin,  $\times 150$ ).

Fig. 7.—Epitrochlear lymph node metastasis (hematoxylin and eosin,  $\times 150$ ).

histologic appearance of the tumor was essentially the same in all the sections from all of the specimens studied, with the single exception of the radius. The metastases in the lymph nodes also showed this structure (Fig. 7). In the radius, cyst formation was noted only occasionally and the tumor freely infiltrated the marrow spaces. Fibrous stroma was abundant only in some of the latter areas (Fig. 8).

The tumor did not show the anaplastic qualities usually associated with malignancy and mitotic figures were rare. New bone formation was observed beneath the periosteum of both the radius and ulna but the tumor did not invade the latter.



Fig. 8.—Photomicrograph showing invasion of the distal part of the radius (hematoxylin and eosin,  $\times 150$ ).

#### COMMENT

This tumor corresponded morphologically with the group of sweat gland neoplasms classified as hydradenoma papilliferum by Gates, Warren, and Warvi, and resembled the lesions reported in the literature as syringadenoma papilliferum or nevus syringadenomatosus papilliferus (Werther<sup>12</sup>) or as hidradenoma (Pick<sup>13</sup>). Not only the local lesions in this case, but even the lymph node metastases had a striking, intracystic papillary structure. Only where it invaded the radius did the tumor tend to lose this appearance and to infiltrate the tissues diffusely.

Gates and associates regard three of their hydradenoid carcinomas as having arisen from pre-existing tumors of the hydradenoma papilliferum type, but they did not maintain a papillary structure throughout. The metastasizing tumor of the vulva reported by Eichenberg appeared to have a similar origin and Hedinger's tumor had a gross papillary configuration, and histologically some portions showed the formation of papillae. The seventeen-year history in the case under discussion,

indicates a relatively low grade of malignancy and suggests that this malignant tumor may have arisen from a cystadenoma.

In addition, this tumor resembled the reported sweat gland carcinomas of proved malignancy in that metastasis was limited to the regional lymph nodes. Similarly, bone invasion has been previously recorded (Morisani<sup>8</sup> and Thierfelder<sup>11</sup>).

The principal consideration in differential diagnosis was metastatic carcinoma, in particular metastasis from a papillary carcinoma of the thyroid gland. However, this appeared to be very unlikely in the light of the clinical course and in view of the abundant mucicarmophilic material present in the tumor.

#### SUMMARY

A malignant sweat gland tumor has been described which arose in the forearm of a 33-year-old Hebrew man. It was first noted when the patient was 16 years old. Over the course of 17 years, it recurred locally four times, invaded the radius, and metastasized to the epitrochlear and axillary lymph nodes. In all of its manifestations, the tumor showed an intracystic papillary structure. At the time of this communication, twenty-two months after pathologic demonstration of bone invasion and extension to the regional lymph nodes, and three months after amputation of the arm, there is no clinical evidence of distant metastasis.

#### REFERENCES

1. Gates, O., Warren, S., and Warvi, W. N.: Tumors of Sweat Glands, *Am. J. Path.* 19: 591-631, 1943.
2. McDonald, J. R.: Apocrine Sweat Gland Carcinoma of the Vulva, *Am. J. Clin. Path.* 11: 890-897, 1941.
3. Eichenberg, H. E.: Hidradenoma Vulvae, *Ztschr. f. Geburtsh. u. Gynäk.* 109: 358-373, 1934.
4. Hedinger, E.: Zur Frage des Plasmocytoms. (Granulations plasmacytom in Kombination mit einem krebzig umgewandelten Schweissdrüsenadenom des behaarten Kopfes), Frankfurt. *Ztschr. f. Path.* 7: 343-350, 1911.
5. Hufschmitt, G., and Diss, A.: Épithélioma Sudoripare, *Bull. Soc. franç. de dermat. et syph.* 36: 503-504, 1929.
6. Moriconi, L.: Adenocarcinoma delle ghiandole sudoripare, *Policlinico (sez. chir.)* 38: 634-642, 1931.
7. Suzuki, S.: Beitrag zur Kenntnis des Schweissdrüsenadenoms, mit besonderer Berücksichtigung seiner histologischen Einteilung, *Jap. J. M. Sc., XIII, Dermat. & Urol.* 2: 165-175, 1941.
8. Morisani: Cited by Loos.<sup>9</sup>
9. Loos, H. O.: Die Carcinome der Anhangsgebilde der Haut, *Arch. f. Dermat. u. Syph.* 174: 465-510, 1936.
10. Diss, A., and Peterschmidt, J.: Épithélioma basocellulaire d'origine sudoripare, *Bull. Soc. franç. de dermat. et syph.* 33: 599-601, 1926.
11. Thierfelder, F. A.: Ein Fall von Schweissdrüsenadenom (Thesis), Leipzig, 1870, O. Wigand.
12. Werther, L.: Syringadenoma papilliferum (Naevus syringadenomatosus papilliferus), *Arch. f. Dermat. u. Syph.* 116: 865-870, 1913.
13. Pick, L.: Über Hidradenoma und Adenoma hidradenoides, *Virchows Arch. f. path. Anat.* 175: 312-364, 1904.

## EXPERIMENTAL OBSERVATIONS ON THE HUMAN ILEOCECAL VALVE\*

CAPTAIN RAYMOND E. BUIRGE,† MEDICAL CORPS, ARMY U. S.

THE reports of Macewen,<sup>1</sup> Rutherford,<sup>2</sup> Short,<sup>3</sup> Bergen, Wesson, and Jackman<sup>4</sup> indicate that the opportunity for prolonged and repeated observations on the ileocecal valve usually do not materialize. White, Rainey, Monaghan, and Harris<sup>5</sup> reported at length upon the nervous control of the sphincter and its reaction to certain drugs. As a result of the thoughtful awareness of Dr. Clarence Dennis concerning my interest in this junction of the alimentary tract, the following observations were made possible on the ileocecal junction of a patient for whom Dennis had necessarily exteriorized a portion of the lower ileum and cecum.

### CONDITIONS OF THE EXPERIMENT

The patient was a 26-year-old French-Indian woman in an excellent state of nutrition. The observations were made two months after the exteriorization procedure, during a period of four weeks prior to a right hemicolectomy. The patient was on a general hospital diet and weighed 121 pounds. No medication was given other than that required for these experiments. Observations were usually continuous from 8:00 A.M. for a period of ten to twelve hours, with occasional rest periods.

The cecum was open, and attached to the abdominal wall in such a fashion as not to permit encroachment of the parietes upon the terminal ileum or the ileocecal valve. Approximately 10 cm. from the valve the lower ileum were exteriorized and completely cut across so that all intestinal content was evacuated through a proximal external ileal fistula. No intestinal content was transported by way of the distal ileal loop into the cecum. In the immediate area of the proximal fistula were numerous loops of small intestine with fistulous openings from which intestinal content escaped.

### THE ILEOCECAL EMINENCE

The lips of the valve were thin, 2 to 5 mm. thick, depending upon the state of contraction. The superior lip projected from the cecal wall 3.5 cm. and the inferior lip 2.5 cm. The aperture varied in size and shape, depending upon the state of activity. At rest it was a narrow transverse, oval orifice 3.0 cm. long, with the frenulum distinctly visible. When contracted it appeared erectile, broader at its attachment to the

\*Aided by a grant from the Graduate School, University of Minnesota.

†On a leave of absence from the Department of Surgery, University of Minnesota Medical School.

Received for publication, Dec. 10, 1943.

cecal wall, and gently tapering to a rounded extremity 2.0 cm. across with the orifice closed and bounded by an everted border of puckered mucosal folds.

The ileocecal prominence was normally a deep pink in color, and generally in a semirelaxed state whether the patient were awake or asleep, except immediately before and during eating, when propulsive and segmental activity became evident by contraction of the entire structure and lengthening and shortening as it appeared to project and retract. At times a gelatinous mucous secretion would be actively extruded through the lips.

Palpation of the contracted structure revealed that the apex consisted of soft yielding tissue (the arches\* of the frenulum) which would admit the tip of the finger with slight resistance. Within the lumen, and for approximately 1.0 cm., an increase in resistance was noted which could be overcome by gentle pressure. Just beyond this area, for a depth of 2.0 cm., a region of contraction was encountered beyond which the finger could not be passed until relaxation occurred. Persistent effort to do so caused the patient pain, which was referred to the epigastrium, and damage to the mucosa as evidenced by tears in the ileal mucosa and slight hemorrhage. When relaxed, the limits of these areas could not be recognized.

#### TYPE OF ILEOCECAL VALVE

The medial and lateral frenula of the valve were plainly visible, except when the ileocecal structure was completely relaxed. The medial frenulum was formed by the medial superior and medial inferior arches\* of the valve. The lateral frenulum appeared to have divided into separate lateral inferior and lateral superior arches (Fig. 1), however after examination in the fresh state and later after fixation, the lateral superior and inferior arches were observed to form the lateral frenulum (type I ileocecal valve).

#### APPARATUS

Satisfactory kymograph records were obtained with Elliott's balloon applicator connected to a spirometer type volume recorder with a writing lever. Tandem balloon records were obtained by an independent balloon-tambour system\* attached to the Elliott applicator, so that both balloons were spaced independent of each other and used as a single instrument. The Elliott system, when filled with 7.0 c.c. of air, exerted a pressure sufficient to sustain an 8.0 to 10.0 cm. column of water.

#### SPONTANEOUS ACTIVITY OF THE TERMINAL ILEUM

Qualitative and quantitative control studies of spontaneous activity of the extramural terminal ileum, the sphincter, and ileocecal valve were

\*The word arches, as applied here and in a previous publication\* was suggested by Edward A. Boyden, Professor of Anatomy, University of Minnesota Medical School.



recorded during twenty periods of 30 to 120 minutes. Additional control records were obtained between the drug experiments.

Control records revealed that there were periods of quiescence and activity in all three areas. The activity of the segments varied, but at times all the segments were quiet. During periods of motility the proximal exteriorized small bowel loops were equally and similarly active, expelling intestinal content. At no time was spontaneous activity in the ileocecal lips, sphincter, or extramural terminal ileum noted independent of activity in the proximal ileal loops.

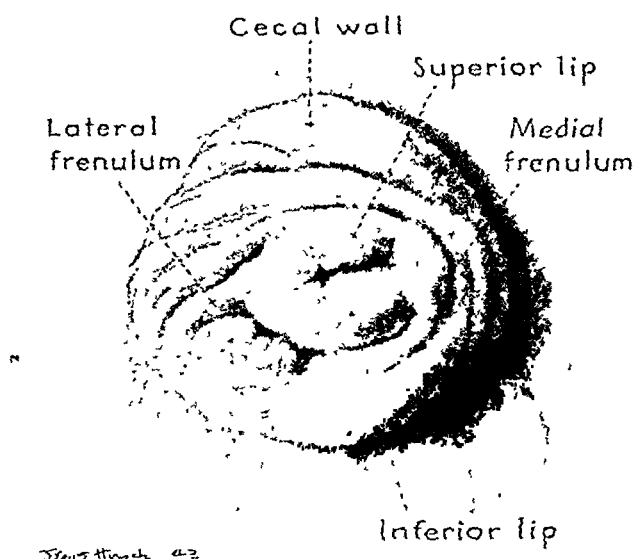


Fig. 1.—Artist's sketch of the ileocecal valve and the cecum.

The extent and frequency of contractions varied, being most energetic in the morning and less active in the evening. Propulsive activity constituted a small fraction (10 per cent) of the total motility which was nonpropulsive, with varying states of tone. At times activity of the sphincter consisted of continuous contractions and relaxations over a period of an hour, then the interval between contractions would lengthen until twenty to thirty minutes would expire. During such times a semi-relaxed state would be effected. During evacuation at the proximal fistula (usually two to three hours after a meal) a short comparable period of sphincter and valve motility occurred followed by relaxation of the entire intracecal portion of the terminal ileum.

#### EFFECT OF MECHANICAL STIMULATION

The valve or sphincter was not observed to maintain a state of prolonged steady contraction, or spastic tonus. Several hundred contractions were recorded from different areas of the intramural and intracecal terminal ileum. The range of duration of contraction was

ten seconds to three minutes. The greatest reaction to any stimulus resulted when a stream of water or a foreign body was introduced into the orifice of the valve.

Introduction of the finger into the relaxed structure produced a contraction along the entire extent of the intracecal portion of the terminal ileum, which grasped the finger at once and held it steadily.

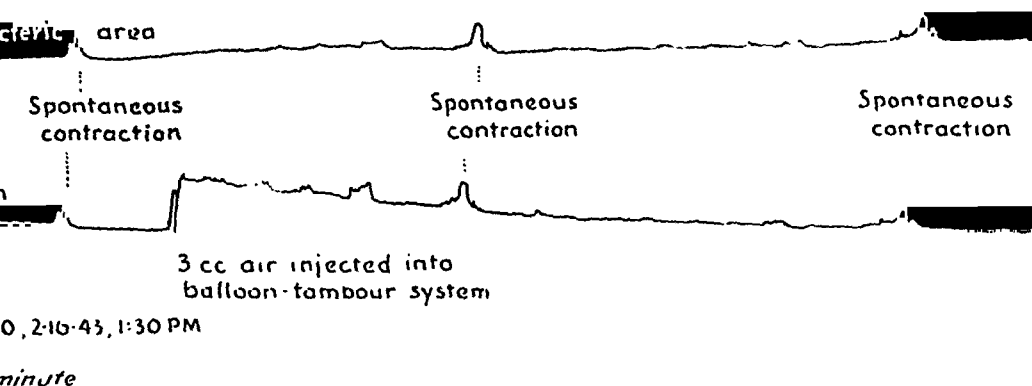


Fig. 2.—Tandem balloon kymograph tracing of the spontaneous activity of the ileum and ileocecal sphincter. There are independent spontaneous contractions in both areas. Air was injected into the ileal balloon system to test the independence of the two systems. Identical types of waves occurred in the ileum and sphincter area, reproduced by different recording systems.

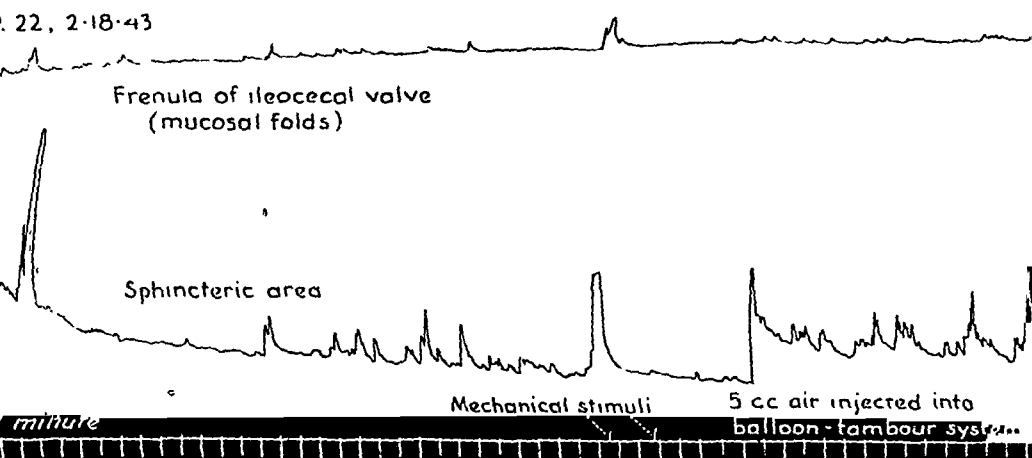


Fig. 3.—Kymograph tracing of the activity of the ileocecal valve and the ileocecal sphincter. Spontaneous independent contractions and contractions resulting from mechanical stimulation occur simultaneously in both structures. The injection of 5 c.c. of air into the balloon-tambour system illustrates the independence of the two balloons residing within the sphincter and within the lips of the ileocecal valve.

Ileal waves could be felt blending into or dying out as they reached an area of increased contraction at the intramural portion of the terminal ileum. Momentarily the grip was firm, then longitudinally and circumferentially segmental areas would slightly relax and con-

tract. Shortly, a definite propulsive wave from the ileum would pass through the entire structure, terminating by contraction of the valvular lips. A pause of relaxation ensued, then the cycle would repeat with somewhat less intensity.

A gentle brush of the mucosa of the cecum or either frenulum would produce a contraction of the valve, and sphincter, after two to three minutes relaxation would be complete except for numerous segmental movements of the valvular lips. A strong stimulus would produce in the patient a vague epigastric distress, which at times amounted to pain. This subjective complaint preceded the actual contraction by three to five seconds. During such a contraction the orifice would be tightly closed, preventing the introduction of an instrument without damaging force.

Twelve periods of thirty to ninety minutes were utilized to record the results of mechanical stimulation. The application of any adequate stimulus, such as stretching by the introduction of an instrument into the sphincter area, was followed by a latent period of two to twenty seconds before contraction started. A summation of stimuli could be produced at the time of the original stimulus and in the early phase of contraction. During the phase of relaxation the structure was not constantly refractory, as contractions could be produced, but these were not as strong as the initial responses. During the recovery period no prediction of its duration could be made, as often considerable time would elapse during which the structure was refractory to all forms of stimuli. The irritability of the area was generally the same for the period observed, although fatigue or adaptability was observed to occur after a particularly active sequence of events. The best results were obtained when the patient was enthusiastic about the work to be done. Bad news or disagreeable circumstances noticeably inhibited the activity of the small intestine, sphincter, and valve. Occasionally experiments were suspended or postponed due to marked reduction in irritability.

#### ELECTRICAL STIMULATION

Stimulation with a constant break and rapid tetanizing current of a Harvard inductorium, using the device of Boyden<sup>9</sup> which consisted of a standard Rehfuss tube transformed into an electrode by inserting a copper wire through the oral end of the rubber tubing and connected to the primary of the inductorium, and the secondary coil connected to a moist lead electrode on the patient's arm, failed to produce a contraction when applied to the mucosa of the cecum, of the intramural terminal ileum, of the sphincter area, or the ileocecal valve (Fig. 4). Induced current stimuli were accompanied by contraction of the ileum when the electrode was placed proximal to the intramural portion of the terminal ileum. Inconclusive results attended a second experiment using fine silver wire clips as the primary electrode.

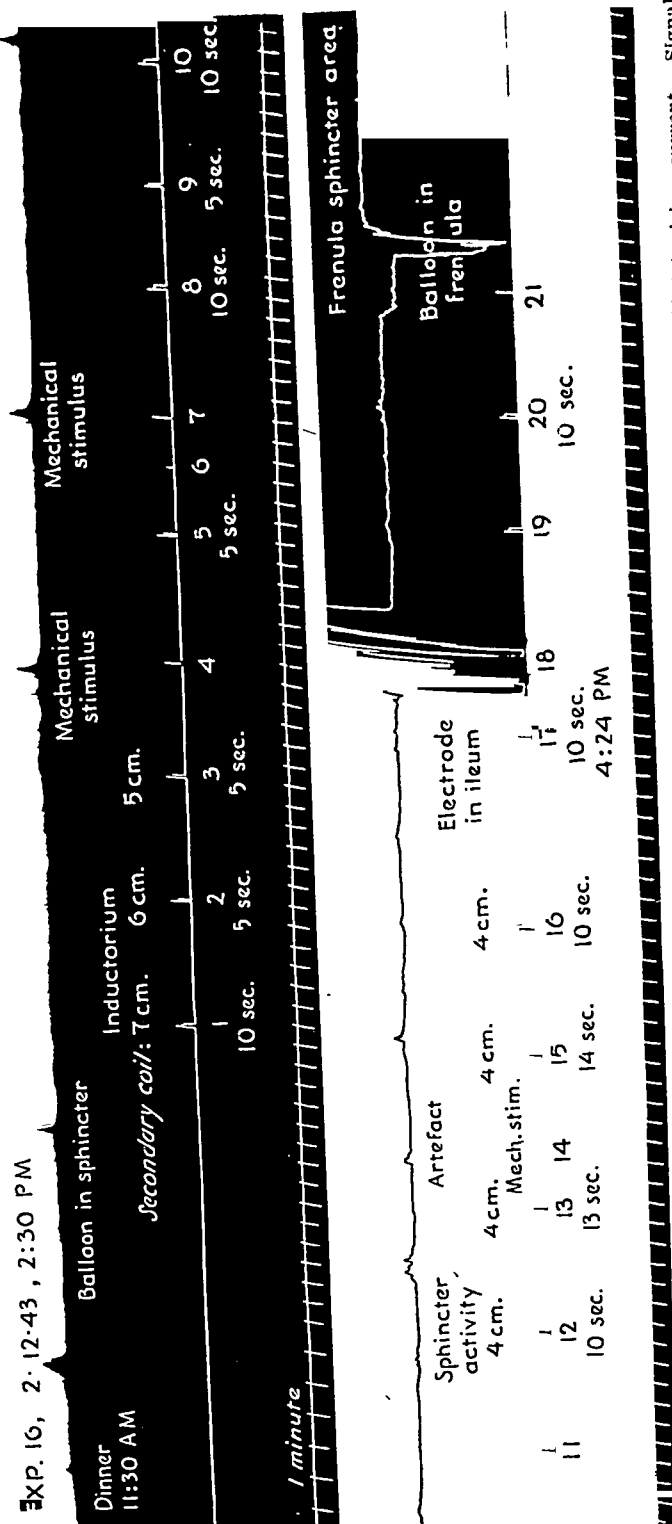


Fig. 1.—Kymograph tracing of the effect attending stimulation of the ileocecal valve and sphincter with a rapid tetanizing current. Signal marker lined up with spirometer lever. Inductorium connected in series with signal marker. 1. Stimulation of terminal ileal opening. 2. Position 6 cm. electrode in terminal ileum. 3. Olive tip extruded from terminal ileum. 4. Olive tip introduced along side of balloon. 5. Stimulation 6. Removal (wave) of balloon from ileocecal valve. 7. Contraction resulting from introduction of olive tip into medial recess of ileocecal valve between medial frenula and the Elliott applicator. 8. No reaction. 9. No reaction. 10. Reaction after few seconds, likely induced contraction. 4 cm. 10 sec. (counted seconds). (All stimuli timed by Edward A. Boyden.) 11. Tetanizing current, 1 cm. 12 sec. No reaction. 12. Removal of bowel content from abdominal wall resulted in some contraction. 4 cm. 10 sec. Patient stated that she had vague pain or distress in epigastrium which was not noticed when currents of less than 1 cm. were used. 13. No reaction. 4 cm. 10 sec. Referred pain to epigastrium. 14. Removal of olive tip from area of activity about four minutes after No. 12 stimulus. 15. Epigastric distress; no contraction, 4 cm. 13 sec. 16. Very slight contraction. 4 cm. 10 sec. 17. Electrode introduced into proximal ileum. 18. Spontaneous contraction forced balloon out of sphincter. Air cell broken and readjusted. 19. Electrode placed in the ascending colon. Segmental contractions. Referred pain to epigastric area. 20. Stimulation of the cecal wall 1 cm. 10 sec. No reaction. 21. Balloon pulled out of sphincter into the valvular lips.

RESPONSE OF THE EXTRAMURAL TERMINAL ILEUM, ILEOCECAL SPHINCTER,  
AND ILEOCECAL VALVE TO DRUGS

The generally persistent area of sphincter contraction lay internal to the ileocecal valve (mucosal lips) and at, or slightly distal to, the extramural portion of the terminal ileum and occupied an area of approximately 2.0 cm. in length. A number of drugs commonly used on surgical patients were employed (Table I). Control records of from twenty to sixty minutes were obtained before the drugs were administered.

*Morphine Sulfate*.—Over a period of seven minutes, .015 Gm. of morphine sulfate was administered intravenously. The patient was asleep thirty minutes later. During this interval the proximal loops showed an increase in tonus and motility. Both segmental and propulsive areas increased in strength and regularity. The terminal ileum, sphincter, and valve showed a decided diminution of motility until the activity present was represented by small segmental waves, with increasing weakness and loss of tonus until at the end of an hour the sphincter was completely relaxed and the ileocecal structure was prolapsed upon the abdominal wall. The sphincter and valve were refractory to mechanical stimuli as repeated stimulation of the cecal wall, the lips of the valve, or the frenula failed to produce a response.

*Amyl Nitrite*.—The inhalation of 0.3 Gm. of amyl nitrite accompanied by pronounced systemic reaction with depression of the systolic blood pressure was without conclusive effect except in one experiment, when it was used successfully in relaxing a persistent painful segmental spasm of the extramural terminal ileum which followed the injection of 1 c.c. of pituitary extract.

*Papaverine Hydrochloride*.—Papaverine hydrochloride, .032 Gm., administered intravenously was followed by an increase in activity of the small intestine. Contractions of the sphincter were unaffected during an interval of normal activity, followed by increased motility and tonus.

*Adrenalin*.—Adrenalin hydrochloride, administered subcutaneously in physiologic doses, abolished all activity of the sphincter and valve and rendered the entire structure refractory to mechanical stimulation. Five experiments in which the general systemic reaction was adequate, and once severe, indicated without exception complete relaxation of the ileocecal valve and sphincteric structure. The extramural portion of the terminal ileum and the proximal ileal loops relaxed with a cessation of segmental and propulsive movements.

*Ephedrine Sulfate*.—Ephedrine sulfate, .05 Gm., applied to the cecal mucosa of the ileocolic eminence resulted in immediate inhibition of segmental and propulsive action of the valve and sphincter.

*Epinephrine Hydrochloride*.—Epinephrine hydrochloride, .06 c.c. (1:1000) subcutaneously, suppressed all spontaneous motility of the

intestine, sphincter, and valve. A diminution in tonus was evidenced by marked relaxation of the valve and sphincter during which time the ileocecum was refractory to all stimuli.

*Pilocarpine*.—Spontaneous activity of the sphincter and the valvular lips was observed for seventy minutes, during which time the motility of the sphincter and lips was generally equivocal. Mechanical stimulation resulted in contraction in both areas. Following the subcutaneous injection of 0.6 c.c. of adrenalin, there was complete cessation of all activity. Twenty minutes later, immediately after the injection of .006 Gm. of pilocarpine, there followed resumption of segmental waves in the valve while the sphincter was somewhat slower to resume activity.

*Strychnine Sulfate*.—Strychnine sulfate, .002 Gm. dissolved in 2 c.c. water and applied to the cecal mucosa of the ileocecal eminence, inhibited contractions of the sphincter. The experiment was not repeated.

*Atropine Sulfate*.—Atropine sulfate, .0005 Gm. subcutaneously following the establishment of augmented motility after the injection of 1 c.c. prostigmine methylsulfate, produced an immediate inhibition of propulsive and nonpropulsive activity in the terminal ileum and sphincter.

*Prostigmine Dimethyl Carbonic Ester of Oxyphenyl-trimethyl Ammonium Methylsulfate*.—One cubic centimeter subcutaneously increased peristaltic activity in the ileum, the proximal small bowel loops, and the sphincter. The increased motility persisted for one to two hours. At another time adrenalin hydrochloride, 0.6 c.c. (1:1000) subcutaneously, resulted immediately in an antagonistic effect on the increased propulsive and nonpropulsive motility of the intestine, sphincter, and valve produced by prostigmine methylsulfate.

*Acetyl-Beta-Methylcholine Chloride (Mecholyl)*.—Twenty-five milligrams intravenously following a forty-minute interval of spontaneous activity resulted in complete cessation of all activity and relaxation of the sphincter. Normal mobility was resumed at the end of four hours.

*Pituitrin (Posterior Pituitary Extract)*.—Pituitrin, 1 c.c. intramuscularly, was accompanied in two experiments by increased propulsive and nonpropulsive activity of the intestine, sphincter, and valve. The patient complained of "gas pains." The response occurred promptly and lasted approximately two hours. On another occasion 1 c.c. of pituitrin was administered intramuscularly after a meal. Propulsive and segmental motility occurred promptly in the three areas, especially the extramural terminal ileum in which a segmental spastic contraction occurred in the area of one balloon lasting twenty minutes producing intense pain. This was relieved after relaxation of the spastic contraction which followed the inhalation of amyl nitrit

TABLE I  
QUALITATIVE AND QUANTITATIVE DATA PERTAINING TO THE ACTION OF DRUGS ON THE ILEOCECAL VALVE, THE ILEOCECAL SPINCTER,  
AND THE ILEUM

Frequency of contractions recorded per unit of time in minutes before and after drug

SUBSTANCE	ILEOCECAL VALVE			ILEOCECAL SPINCTER			TERMINAL ILEUM		
	BEFORE		AFTER	BEFORE		AFTER	BEFORE		AFTER
	TIME	NO.		TIME	NO.		TIME	NO.	
Morphine sulfate	Active		Suppressed	30	7	0	Active		Inhibited motility
Papaverine hydrochloride	Active		Unchanged	60	5	19	Active		Increased motility
Adrenalin	50	4	50	0	11	1	Active		Inhibited
Adrenalin hydrochloride	Active		Quiet	70	5	0	Active		Reduced motility
10 min. later: Amyl nitrite	Inactive		Active segmental motility	40	0	3	Inhibited		Segmental motility
Epinephrine sulfate	Active		Inhibited activity	45	5	2	Active		Inhibited motility
Epinephrine hydrochloride	Active		Complete suppression	70	8	1	Active		Suppressed motility
Pilocarpine	50	2	50	50	0	14	Active		Increased motility
Strychnine sulfate	Active		Inhibited	40	8	5	Active		Inhibited motility
Atropine sulfate	Active		Inhibited	80	11	5	Active		Inhibited motility
Prostigmine	Active		Augmented	20	2	6	20	4	20 11
Mecholyl	Active		Suppressed	40	6	1	Active		Suppressed
Pituitrin	Active		Augmented	45	6	13	Active		Evacuation proximal loops

## EFFECT OF DISTENTION OF THE COLON

The sphincter's contractile and segmental activity was inhibited (Fig. 5) during the introduction, and particularly after the distention incidental to a saline enema of 1,500 c.c.

## EFFECT OF INCREASED INTRAVESICAL PRESSURE

By means of a balloon residing in the urinary bladder and connected to a mercury manometer and water system, the intravesical pressure was increased without reflux into the ureters. The activity of the valve, sphincter, and ileal loops was reduced (Fig. 6) by increment of the intravesical pressure.<sup>10, 11</sup> Augmentation of activity followed the release of intravesical pressure.

## SUMMARY

The factors which determine the state of closure of the ileocecal sphincter such as the pressure of material in the bowel, that is distention, were not operative in this patient as all intestinal content introduced orally was shunted to the exterior through a proximal fistula.

It was observed that retraction or shortening of the ileocecal structure occurs when the segments are coordinated to accept a propulsive wave from an adjacent segment. The ileocecal valve during a propulsive contraction is obliterated by retraction of the frenula and the disappearance of the mucosal folds of the valve as they are retracted over the contracted musculature of the intracecal terminal ileum. A nonpropulsive or segmental wave is not associated with shortening of the active segment and the valve is not obliterated. The ileocecal valve is most readily visualized during periods of inactivity or diminution of tonus in the sphincter area.

The ileocecal valve is generally considered to have a passive mechanical function dependent<sup>12</sup> upon a complete frenulum (type I ileocecal valve was found<sup>6</sup> to occur in 54 per cent of 500 human cecums) and increased intracecal tension whereby the lateral and medial frenula are made taut, closing the arches of the valve. In addition to this adynamic action of the ileocecal mucosal folds, the valve has been shown to be capable of approximation of the lips by muscular contraction (Figs. 1 and 2). Independent contraction of the valvular lips and sphincter resulted by varying the intensity of the stretch stimulus. In addition to the records of contraction the examining finger has been gripped by the mucosal lips.

The observations of Wesson,<sup>13</sup> and White and associates<sup>5</sup> were confirmed as to the presence of a definite contracting muscular band within the cecal portion of the terminal ileum proximal to the mucosal lips. Boyden examined this area and suggested it may be located in the aperture of the colon where the ileum passes through the cecal wall. When contracted the intestinal lumen completely excludes the introduc-



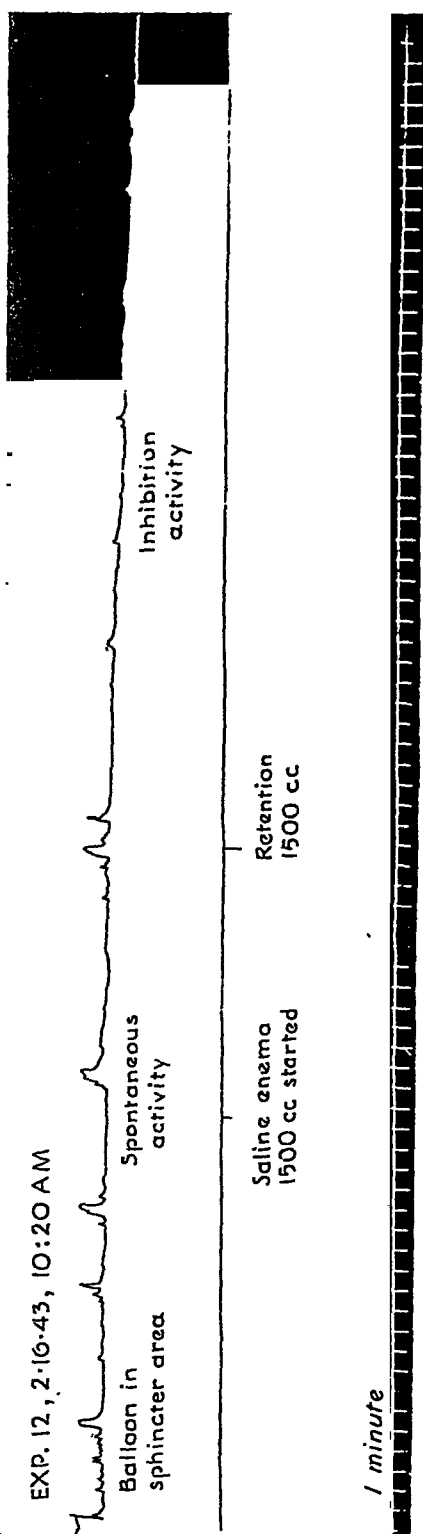


Fig. 5.—Kymograph tracing illustrating the inhibition of the ileocecal sphincter following increased intracolonic pressure.

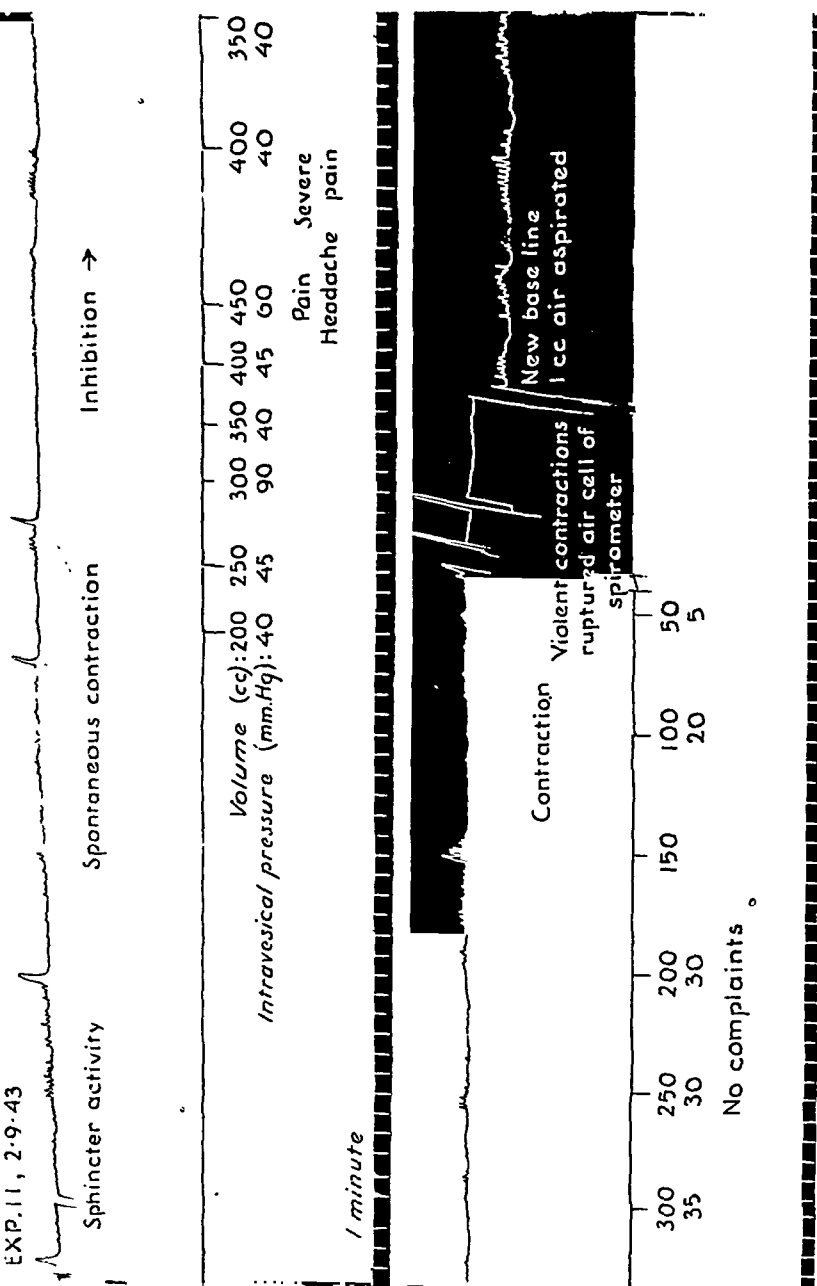


Fig. 6.—Kymograph record of the effect of increased intravesical pressure on the motility of the ileocecal valve and sphincter. Signal marker and spirometer lever were synchronized. The bladder was distended at the rate of 15 c.c. per minute. Inhibition occurred when 300 c.c. or a vesical pressure of 90 mm. Hg was obtained. This pressure was momentary and quickly dropped to 60 mm. Hg. Activity was not completely suppressed. Inhibition lasted for forty-five minutes when a spontaneous contraction occurred. As the bladder was emptied a violent series of contractions ruptured the air cell of the spirometer. Subsequently the activity became steady but less vigorous. During the period of inhibition, quiescence of the proximal ileal loops persisted.

tion of an instrument beyond the sphincter without a force far exceeding the pressures found by Wangenstein<sup>14</sup> and Sperling<sup>15</sup> within the colon in cases of colonic obstruction. Rutherford, White and co-workers, and Wesson have mentioned the difficulty of forcing the sphincter from the cecal side. An opportunity to determine the resistance of the sphincter from the ileal as well as the cecal side was overlooked in this study.

The inhibitory effect of increased intraluminal tension, intracolonic and intravesical pressure, upon the contraction of the sphincter may upon occasion be one of the physiologic factors underlying incompetency of this junction when the type of ileocecal valve due to its variable structure would not justify an expectation of competency.

The reports of others<sup>7, 16, 17, 18</sup> have repeatedly indicated the species difference of the reaction of the sphincter and valve to adrenergic substances. The reaction of the human ileocecal valve and sphincter following the injection of epinephrine-like substances and other drugs justifies the assumption that these structures behave not unlike the small intestine. Wesson<sup>13</sup> and I<sup>19</sup> agree that the presence of an extracircular muscle in a large number of embryonic and adult specimens of the intracecal terminal ileum was not observed upon microscopic examination of innumerable serial sections.

#### CONCLUSIONS

Experimental results indicate that the mechanical, hormonal, and local reflexes of the ileocecal valve and sphincter are so adjusted as constantly to produce responses identical with those of the small intestine to adrenergic and cholinergic drugs.

The balloon method of investigation failed to reveal any fundamental distinctions in the behavior of the ileocecal valve, the ileocecal sphincter, and the small intestine.

The apparent similarity of activity in the extramural terminal ileum, sphincter, and of the intracecal terminal ileum and the ileocecal valve gives rise to the need for further interest in the physiology of this area.

The presence of an area of increased contractility was observed within the cecal portion of the terminal ileum.

Prolonged tonic contractions, characteristic of sphincter action, were not observed.

#### REFERENCES

1. Macewen, William: The Function of the Cecum and Appendix, *Lancet* 2: 995-1000, 1904.
2. Rutherford, A. H.: The Ileocecal Valve, London, 1914, H. K. Lewis & Co. Ltd.
3. Short, A. R.: Observations on the Ileocecal Valve in Man, *Brit. M. J.* 2: 164-165, 1919.
4. Barga, J. Arnold, Wesson, Harrison R., and Jackman, Raymond J.: Studies on the Ileocecal Junction (Ileocecus), *Surg., Gynec. & Obst.* 71: 33-38, 1940.
5. White, H. L., Rainey, W. R., Monaghan, Betty, and Harris, A. S.: Observations on the Nervous Control of the Ileocecal Sphincter and on Intestinal Movements in an Unanesthetized Human Subject, *Am. J. Physiol.* 108: 449-457, 1934.

6. Buirge, Raymond E.: Gross Variations in the Ileocecal Valve: A Study of the Factors Underlying Incompetency, *Anat. Rec.* 86: 373-385, 1943.
7. Elliott, T. R.: On the Innervation of the Ileocecal Sphincter, *J. Physiol.* 31: 157-168, 1904; The Action of Adrenalin, *J. Physiol.* 32: 401-467, 1904.
8. Miller, T. G., and Abbott, W. O.: Intestinal Intubation: A Practical Technique, *Am. J. M. Sc.* 187: 595-599, 1934; Small Intestinal Intubation; Experiences With a Double Lumened Tube, *Ann. Int. Med.* 8: 85-92, 1934.
9. Boyden, Edward A., and Birch, Carroll J.: II. Response to Faradic Excitation of Stomach, Small Intestine and Cecum, *Am. J. Physiol.* 92: 301-316, 1930.
10. Svien, H. J., and Mann, F. C.: Intestinal Activity Following Distention of the Gall Bladder and Urinary Tract: An Experimental Study, *SURGERY* 13: 67-80, 1943.
11. King, C. E.: Studies on Intestinal Inhibitory Reflexes, *Am. J. Physiol.* 70: 183-193, 1924.
12. Wakefield, E. G., and Friedell, Morris T.: The Structural Significance of the Ileocecal Valve, *J. A. M. A.* 116: 1889-1893, 1941; The Ileocecal Valve of Man, *Proc. Staff Meet., Mayo Clin.* 16: 705-707, 1941.
13. Wesson, Harrison R.: The Ileocecal Junction With Special Reference to the Musculature, Lymphatic Block, and Physiology, University of Minnesota (Oct.), 1937, Thesis.
14. Wangenstein, Owen H.: Intestinal Obstructions: A Physiological and Clinical Consideration With Emphasis on Therapy; Including Description of Operative Procedures, Ed. 2, Springfield, Ill., 1942, Charles C Thomas, Publisher, p. 8-73.
15. Sperling, L.: Role of the Ileocecal Sphincter in Cases of Obstruction of the Large Bowel, *Arch. Surg.* 32: 22-48, 1936.
16. Kuroda, Mikizo: Observations of the Effects of Drugs on the Ileo-colic Sphincter, *J. Pharmacol. & Exper. Therap.* 9: 187-195, 1916.
17. Dale, James: *Physiol.* 24: 179, 1906. Quoted by Kuroda.<sup>16</sup>
18. Henriksen, J., and Ivy, A. C.: Studies on the Ileocecal Sphincter of the Dog, *Am. J. Physiol.* 96: 494-507, 1931.
19. Buirge, Raymond E.: Unpublished data.

## PAPILLOMA OF THE GALL BLADDER

WILLIAM GREENWALD, M.D., NEW YORK, N. Y.

IN REVIEWING the literature on the subject of papilloma of the gall bladder one is immediately impressed with the diversity of opinion as to the occurrence of this pathologic entity.

Kerr and Lendrum<sup>1</sup> in their extensive review of the subject concluded that but twenty-one "authentic" cases had been found up to 1936. Yet, one writer alone, Phillips<sup>2</sup> reported 500 cases of one or more papillomas found in an unstated number of gall bladders removed at the Mayo Clinic in a period of six years from 1923 to 1929. Shepard and associates,<sup>3</sup> in a report on gall bladder tumors in general in 1942, reported forty-five cases under the heading of polypi, which from their pathologic description probably were mostly papillomas. These cases were a collection of the three authors over a period of thirty-two years from 1906 to 1938. Kirklin<sup>4</sup> reported in 1931, that the incidence of papillomas was about 8.5 per cent in more than 1,700 gall bladders removed at the Mayo Clinic over a period of seven years. This publication covered the same period as that of Phillips<sup>2</sup> of the same clinic and shows a marked statistical variance. Kirklin<sup>5</sup> also reported, in 1932, fifty-one cases diagnosed roentgenographically of which fifteen were treated surgically and fourteen were pathologically demonstrated to be papilloma.

In a casual survey among surgeons of my acquaintance and from the records of the hospitals with which I am connected, a single incidence or no knowledge of a single case of this pathologic entity could be recalled. Within a period of six months two such cases have come under my care and were diagnosed preoperatively as papillomas of the gall bladder.

CASE 1.—H. T., a 46-year-old white woman, complained of pain in the right upper quadrant one-half to four hours after meals, particularly after fried or fatty foods had been ingested. Loss of twenty pounds in weight was also reported. The patient was a tripara who was in excellent health up to three years before admission when, because of menorrhagia due to uterine fibroids a hysterectomy had been performed. Following this, surgical menopause associated with moderately discomforting climacteric symptoms occurred. Estrogenic therapy was instituted and the patient was in good health until the initial attack of upper right quadrant pain. About six months before admission the patient had a severe attack of colicky pain in the right upper quadrant radiating around the upper abdomen and backward toward the right scapula. This was accompanied by nausea and vomiting. A physician administered morphine, which relieved the attack. However,

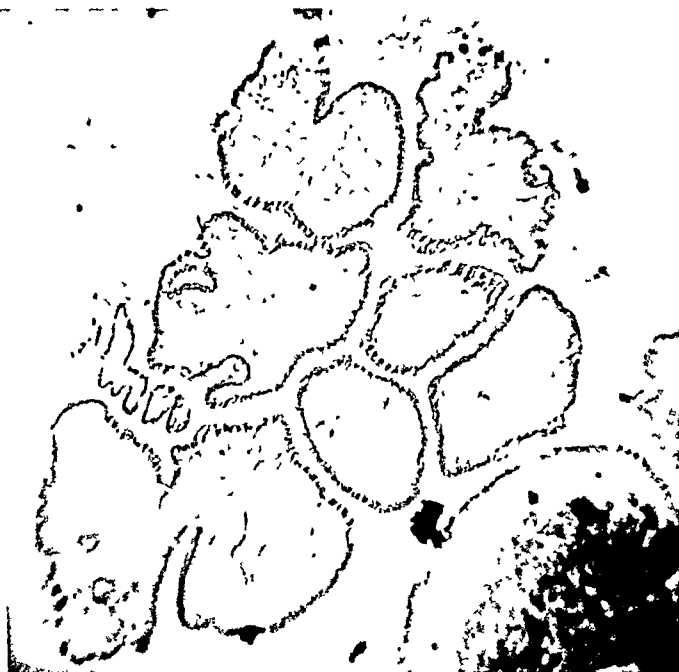


Fig 1

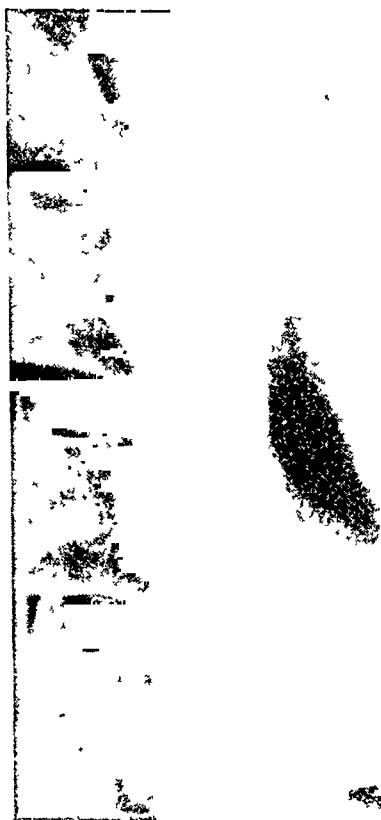


Fig 2

since that time the ingestion of fatty and fried foods caused bloating, sour eructations, and belching. Appetite was poor because of fear lest eating precipitate an attack.

Examination showed apparent loss of weight, slight epigastric tenderness, and midline low abdominal scar. Examination was otherwise essentially normal.

There were no abnormal urinary findings. Hemoglobin was 82 per cent; erythrocytes, 3,800,000; leucocytes, 7,600; polymorphonuclears, 62 per cent (58 per cent segmented and 4 per cent stab); lymphocytes, 35 per cent; monocytes, 2 per cent; eosinophiles, 1 per cent. Gastric analysis showed no free acid in fasting specimen. There was marked hypochlorhydria by the fractional method (Ewald meal), free hydrochloric acid reaching maximum 10 degrees at forty-five minutes, and no abnormal microscopic findings.

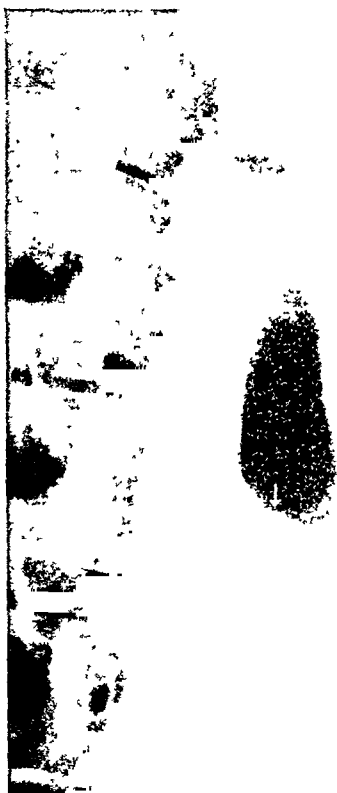


Fig. 3.

Gall bladder series reported by Dr. Frederic Betelheim showed a normal sized and shaped gall bladder, well visualized. There was a small negative shadow remaining in the same relative position in all views. Emptying was slightly delayed. This negative shadow was thought to be a stone or a papilloma. Because of the consistently fixed position of this shadow the latter was considered more likely. Gastrointestinal series revealed no pathology.

Upon operation March 18, 1943, a small thin-walled gall bladder was found which emptied itself easily upon pressure. No stones or growths could be palpated within the fundus. The common duct was explored and revealed no pathology. No other intraabdominal abnormality was seen. Because of the symptomatology and x-ray findings the gall bladder was removed. When opened and



Fig. 4



Fig 5



examined, a pea-sized papilloma was found in an otherwise apparently normal gall bladder. The pathologic report on the specimen submitted was as follows:

Gross examination showed a gall bladder 5 cm. long by  $1\frac{1}{2}$  cm. wide at mid-portion. The thickness of the wall averaged 1 mm. The mucosa was diffusely reticulated and there was at the fundus a papilloma the size of a split pea.

Microscopically, the histologic picture presented an edematous fibrous tissue core covered by a layer of low columnar epithelium. At times, continuous papillomatous stalks came together and produced a picture of adenoma. The structure of the individual papillomatous stalks is best seen when cross sections of a few of them are represented in a microscopic field.

The postoperative course was uncomplicated. On subsequent examination the patient's appetite had returned to normal with gain in weight and no further food idiosyncrasies.

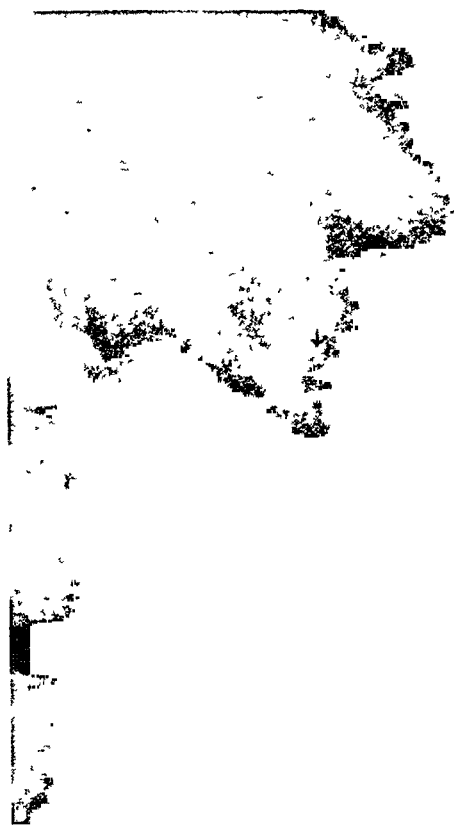


Fig. 6.

CASE 2.—R. K., a 36 year old white married nulliparous woman, complained of slight discomfort after eating. About one week previous to examination the patient had a severe colic in the right hypochondrium accompanied by nausea and vomiting.

The patient had had the usual childhood diseases. Otherwise she had been fairly well except for an attack of appendicitis about eight years before admission for which appendectomy was performed. Following this the patient suffered from constipation and vague gastrointestinal complaints. An operation for "adhesions" was performed about three years before admission, after which the patient stated she felt fairly well except for an occasional attack of indigestion.

About one week previous to admittance the patient had a severe attack of pain in the right upper quadrant. A physician diagnosed the condition as an acute gall stone colic and administered morphine which relieved all symptoms. The patient was referred for surgery with a diagnosis of cholecystitis with cholelithiasis.

Physical examination was essentially negative and blood count, blood chemistry, and urinalysis were normal.

Examination of the x-ray pictures submitted showed a small negative shadow in a well-filled gall bladder which was slightly larger than normal. The gall bladder emptied fairly well after a fatty meal and the negative shadow persisted. The negative shadow was reported as a single stone. However, because of the relatively fixed position of the shadow in all views, a diagnosis of papilloma of the gall bladder was made.

Upon operation, Aug. 2, 1943, numerous adhesions were found although the gall bladder itself was fairly free except for a few small bands between the fundus and the hepatic flexure of the colon. The gall bladder emptied itself easily, was thin-walled, and no stones were palpated within it or in the biliary passages. The organ was removed in spite of its normal appearance because of the roentgenographic findings and previous history of colic. Upon opening the gall bladder a small papilloma was found in the fundus and the mucosa showed a typical picture of the strawberry gall bladder.

*Pathologist's report.*—Pathologic examination of the gall bladder showed a pear-shaped gall bladder  $6\frac{1}{2}$  cm. long and  $3\frac{1}{2}$  cm. wide. The organ had been turned inside out and the mucosa presented a typical strawberry appearance. The wall was edematous and averaged 3 mm. in width. A papillomatous mass the size of a split pea was present on the mucosa. There were no stones.

Microscopically the picture was that of a chronic cholecystitis with a localized papillomatous exerescence. The latter consisted of a layer of epithelium from the mucosa of the gall bladder, investing a core of clear cells filled with lipid.

The postoperative course was uncomplicated and subsequent examination showed the patient to be in excellent health and symptom free.

#### DISCUSSION

In most of the literature reviewed the question of malignancy of papilloma is raised in view of our knowledge that these same tumors occurring in the urinary bladder or gastrointestinal tract very often so manifest themselves. However, except for one case of associated malignancy reported by Phillips,<sup>2</sup> which he believed to be concomitant rather than resultant pathology, no such tendency is noted.

An also singular conclusion reached by most writers is that whereas carcinoma of the gall bladder is usually associated with cholelithiasis, papillomas rarely show such tendency. However, Phillips<sup>2</sup> mentioned stones found in his cases but by his reference to MacCarty's description of "Cholecystitis Catarrhalis Papillomatosis" his cases probably included many of this description.<sup>6</sup> Probably this latter pathologic condition would be found in most acute or acute exacerbations of chronically affected gall bladders. However, this communication is concerned with papilloma occurring as a single tumor or multiple tumors which are not associated with other or only slight pathology. Kirklin<sup>5</sup> pointed out that most of the gall bladders in which he was able to demonstrate papillomas proved, upon subsequent examination after removal, to show only slight or no other concomitant pathology.

As for the pathologic picture itself, probably the best description is that of Ringel,<sup>7</sup> who described the true papilloma of the gall bladder as a framework of vascular connective tissue covered by a single layer of tall columnar epithelium. The tumor may be sessile or pedunculated, measuring from 1 to 5 mm. in diameter. Occasionally clear cells containing refractile neutral fat or cholesterol are found in the connective tissue core.

Symptomatically these patients present a picture simulating any type of gall bladder disease from the simple occasional biliary colic to severe obstruction with jaundice.

Brown and Cappell<sup>8</sup> described a case of chronic obstructive cholecystitis with multiple papillomas. Henry<sup>9</sup> described a case of papilloma of the gall bladder in which a papillary implant was found in the cystic duct. Symptoms of slowly progressive obstruction necessitated operation at which multiple villous papillomas of the fundus were also found.

Another point for conjecture is whether we may not tend to overlook this pathologic entity owing to the failure of visualization of the growth in the roentgenographic picture.

Even at operation it is possible to overlook this pathology as proved by the two cases cited, as the gall bladders in both cases were so normal in appearance, to palpation, and, in response to emptying on pressure, that it was with some reluctance that cholecystectomy was performed.

#### CONCLUSIONS

1. Papilloma of the gall bladder is a rather rare occurrence.
2. Papilloma of the gall bladder may simulate any type of biliary disease.
3. The diagnosis of papilloma of the gall bladder preoperatively can be made only upon roentgenographic study.
4. At operation the gall bladder may appear absolutely normal but should be removed if symptoms of biliary disease were clinically present and if at operation no other intra-abdominal pathology can be found to account for the symptomatology.

#### REFERENCES

1. Kerr, A. B., and Lendrum, Alan C.: Chloride Secreting Papilloma of the Gall Bladder, *Brit. J. Surg.* 23: 615-639, 1936.
2. Phillips, John R.: Papilloma of Gall Bladder, *Am. J. Surg.* 21: 38-42, 1933.
3. Shepard, V., Walters, W., and Dockerty, M. B.: Papilloma of Gall Bladder, *Arch. Surg.* 45: 1-18, 1942.
4. Kirklin, B. R.: Diagnosis of Papilloma of Gall Bladder, *Am. J. Surg.* 25: 1, 1931.
5. Kirklin, B. R.: Papilloma of Gall Bladder, *Proc. Staff Meet., Mayo Clin.* 7: 26, 1932.
6. Personal Communication: Mayo Clinic.
7. Ringel: Ueber Papillom der Gallenblase—*Centralbl. f. Chir.* 26: 129-130, 1899.
8. Brown, F. R., and Cappell, D. F.: Multiple Villous Papillomata of Gall Bladder, *Brit. J. Surg.* 23: 707-717, 1937.
9. Henry, Chas. K. P.: Benign Papillomata of Gall Bladder and Biliary Ducts, *Canad. M. A. J.* 28: 300-302, 1933.

## THE UROBILINOGEN TEST AS AN ADDITIONAL AID IN THE EARLY RECOGNITION OF FECAL FISTULA

IVAN D. BARONOFKY, M.D., MINNEAPOLIS, MINN.

*(From the Department of Surgery, University of Minnesota Hospitals)*

**A**N EXTERNAL colonic fistula is an abnormal communication between the colon and the surface of the body. Such fistulas are called fecal fistulas because they communicate with the colon and discharge intestinal contents and feces. Most of these colonic fistulas are postoperative, only a few occurring spontaneously.

The diagnosis is usually made by the ingestion of aniline dyes, such as Congo red, and the subsequent appearance of these dyes in the discharges. It is the purpose of this article to show how the Ehrlich test for urobilinogen may be used to establish further the diagnosis of a fecal fistula.

The term "urobilin" was first used by Jaffe in 1868.<sup>1</sup> While spectroscopically studying the oxidation products of bilirubin, he noted an undescribed absorption band at about 490 to 500 millimicrons. Because of its occurrence in urine and bile, he called the substance giving this absorption band, urobilin. Van Lair and Masius,<sup>2</sup> in 1871, described a similar pigment in the feces which they called "stercobilin." In 1901, Ehrlich<sup>3</sup> described a color reaction in urine with concentrated hydrochloric acid and p-dimethylaminobenzaldehyde. Neubauer,<sup>4</sup> in 1903, noted that fresh urine gave a positive Ehrlich reaction, but no urobilin absorption spectrum. On standing, as the Ehrlich reaction became weaker, the urobilin absorption spectrum became progressively stronger. He also showed that the reduction of noncrystalline urobilin with sodium amalgam yielded a chromogen with a strongly positive Ehrlich reaction. Bauer,<sup>5</sup> in 1905, reduced bilirubin obtained from cattle gallstones with sodium amalgam. The resulting chromogen gave a strongly positive Ehrlich reaction, thus demonstrating further the relationship of bilirubin, urobilinogen, and urobilin. Le Nobel<sup>6</sup> as early as 1881 had made studies of this chromogen and called it "urobilinogen." Friedrich Von Mueller<sup>7</sup> in a classical experiment demonstrated the enterogenous origin of urobilin and its enterohepatic circulation. He fed hog bile to a patient with a complete biliary obstruction. On the second and third days, respectively, urobilin appeared in the feces and then in the urine. The experiment was then repeated with urobilin-free bile and the same results obtained. McMaster and Elman<sup>8</sup> many years later confirmed these results. The hepatogenous theory of the origin of urobilin, of which the French workers were adherents, has practically been abandoned. Meyer-Betz<sup>9</sup> points out the fact that although disproved, the hepatogenous theory

continued to hold the interest of these men for at least two decades. Gerhardt,<sup>10</sup> in 1897, described the occurrence of urobilinogen in pleural, pericardial, and peritoneal exudates. The bacterial reduction of bile pigments to form urobilinogen has been demonstrated by various observers. Von Mueller<sup>7</sup> showed that on standing, bile bilirubin decreased and the bile urobilin increased. Maly,<sup>11</sup> and Kammerer and Miller<sup>12</sup> showed that one may produce urobilin *in vitro* by inoculating sterile urobilin-free bile. McMaster and Elman<sup>8</sup> have been able to accomplish the same *in vivo*, by putting particles of stool into the previously sterile biliary tracts of dogs.

Fischer<sup>13</sup> gave us the first concrete knowledge of the chemistry of this group of substances. He showed that bilirubin was converted by simple reduction to mesobilirubinogen, which on exposure to light and air gave urobilin characteristics. It remained for Watson<sup>14-17</sup> to isolate crystalline stereobilin from both human feces and pathologic human urine. He then demonstrated that crystalline urobilin prepared from mesobilirubinogen differed from stereobilin in a number of respects.<sup>18, 19</sup> Siedel and Meier<sup>20</sup> then synthesized this compound and called it urobilin IX a. Human bile samples that are reduced with amalgam result in urobilinogen which upon conversion yields urobilin IX a.<sup>21</sup> Watson, Sborov, and Schwartz,<sup>22</sup> in determining whether stereobilin is derived from mesobilirubinogen, have recently shown that the output of stereobilin is greatly increased in the feces when mesobilirubinogen was given by mouth. It is reasonably certain that this conversion of mesobilirubinogen to stereobilin is probably related to bacterial action. An interesting advance was made recently by Watson and Schwartz<sup>23</sup> who showed that on addition of bile and mesobilirubinogen to acholic feces, one may cause stereobilin formation in some feces, and a dextro-rotatory urobilin in others. Normal stereobilin is levorotatory, and this knowledge added to the finding that d-urobilin may be obtained in infected bile samples to which mesobilirubinogen has been added indicates that some unknown factor may influence the direction of conversion.<sup>24</sup> Previously, Watson<sup>25</sup> had shown that the color intensities of mesobilirubinogen-aldehyde and stereobilinogen-aldehyde, as developed by his modification of Terwen's method, were identical.

With this in mind it was thought that the Ehrlich reaction, which is given by mesobilirubinogen and stereobilinogen, might be used in suspected cases of fecal fistula. To 2 or 3 c.c. of the discharge of the suspected fistula in a test tube, an equal amount of Ehrlich's reagent (p-dimethylaminobenzaldehyde) was added. Two volumes (to one of the material being tested) of a saturated solution of sodium acetate were then added.<sup>26</sup> A pink to red color indicated the presence of an urobilinogen.

This procedure was used on the following cases:

CASE 1.—E. N. (University Hospital No. 732750) had had a resection of a tumor of the colon which had extended into the bladder. This necessitated resec-

tion of the colon and partial resection of the bladder including division and ligation of the left ureter. Penrose drains were inserted. Postoperatively her course was rather stormy. Much discharge was observed from the drains. A question arose as to whether there may be a urinary fistula, a fecal fistula, or both. Five cubic centimeters of the discharge were tested for urobilinogen, and a positive reaction was obtained. The urine showed no urobilinogen. While this did not eliminate the possibility of urinary fistula it was evident that fecal contents were present. Congo red was ingested and was observed the next day on the dressings, further establishing the presence of fecal fistula. At post-mortem examination, eleven days after operation, communications were seen to exist between the external skin surface where the drains had been placed and the bladder and colon.

CASE 2.—H. S. (University Hospital No. 732767) also had a colon resection for tumor. The discharge of drainage areas was again tested and a positive urobilinogen test was obtained. On post-mortem examination a fecal fistula was found.

CASE 3.—Mrs. H. S. (University Hospital No. 734917) had a resection of a segment of ileum for closed loop obstruction occasioned by a perforation of an ulcerative enteritis. Postoperatively the skin wound broke down and a purulent discharge was obtained. The possibility of a fistula was entertained. However, the test for urobilinogen and bilirubin was negative on some of the exudate. Congo red was given and was not observed on the dressing. On post-mortem examination no fistula was found.

#### COMMENT

Although we have not used the Ehrlich test in cases of small bowel fistulas, it would seem that the Gmelin color play with yellow nitric acid might be used on discharges in addition to the Ehrlich test. Bilirubin, mesobilirubin, and biliverdin will give a positive Gmelin reaction. The Ehrlich test will be positive if there is any urobilinogen present. No reference has been found in the literature to the use of these tests in cases of intestinal fistulas.

In the case of a colonic fistula wherein the jaundice is due to a complete, unremitting obstruction such as carcinoma of the head of the pancreas, the Ehrlich test would probably not be of any use. Such a combination would be most unusual, however.

The value of the testing of discharges of fecal fistulas would be in the following:

1. Early recognition, that is, the examination of a material already escaping from the wound as contrasted with the observation of escape of material from the wound only after ingestion of charcoal or Congo red.
2. In the presence of intestinal paresis, the delay in transit would not invalidate the test, as it may with charcoal and Congo red.

#### SUMMARY AND CONCLUSIONS

The Ehrlich test for urobilinogen is suggested as an additional diagnostic aid in the diagnosis of external colonic (fecal) fistulas. Three

cases are presented, in two of which the findings were corroborated by autopsy findings, and in the third a negative test was also confirmed by absence of fistula at autopsy.

## REFERENCES

1. Jaffe, M.: Beitrag zur Kenntnis der Gallen und Harnpigmente, *Centralbl. f. d. med. Wissensch.* 6: 241-245, 1868.
2. Van Lair, C. F., and Masius, J. B.: Ueber einen neuen Abkömmling des Gallenfarbstoffes im Darminhalt, *Centralbl. f. d. med. Wissensch.* 9: 369-371, 1871.
3. Ehrlich, P.: Ueber die Dimethylaminobenzaldehydreaction, *Med. Woche* 1: 151-153, 1901.
4. Neubauer, O.: Ueber die Bedeutung der neuen Ehrlichschen Farbenreaktion (mit Dimethylaminobenzaldehyde), *München. med. Wchnschr.* 50: 1846, 1903.
5. Bauer, R.: Die Ehrlichsche Aldehydreaction in Harn und Stuhl, *Centralbl. f. inn. Med. Nr.* 34, 1905.
6. Le Nobel, C.: Ueber die Einwirkung von Reduktionsmitteln auf Haematin und das Vorkommen der Reduktionsprodukte im pathologischen Harn, *Pflüger's Arch. f. d. ges. Physiol.* 40: S. 501, 1887.
7. Von Mueller, F.: Ueber Icterus, *Jahresb. d. schles. Gesellsch. f. vaterl. Kult.* 70: 1, 1892.
8. McMaster, P. D., and Elman, R.: Urobilin Physiology and Pathology, *Ann. Int. Med.* 1: 68-73, 1927.
9. Meyer-Betz, F.: Die Lehre vom Urobilin, *Ergebn. d. inn. Med. u. Kinderh.* 12: 733, 1913.
10. Gerhardt, D.: Ueber Urobilinur, *Ztschr. f. klin. Med.* 32: 303, 1897.
11. Maly, R.: Untersuchungen ueber die Gallenfarbstoffe, dritte Abhandlung, Umwandlung von Bilirubin in Harnfarbstoffe, *Ann. Chem.* 163: 77, 1872.
12. Kammerer, H., and Miller, K.: Zur enterogenen Urobilin Bildung, *Deutsches Arch. f. klin. Med.* 141: 318, 1923.
13. Fischer, H.: Zur Kenntnis der Gallenfarbstoffe über Mesobilirubinogen, *Ztschr. f. Biol.* 65: 163-182, 1914.
14. Watson, C. J.: Ueber Stercobilin und Porphyrine aus Kot, *Ztschr. f. physiol. Chem.* 204: 57-67, 1932.
15. Idem: Ueber Stercobilin, Kopromesobiliviolin und Kopronigrin, *Ztschr. f. physiol. Chem.* 208: 101-119, 1932.
16. Idem: Isolation of Crystalline Urobilin From Human Urine, *Proc. Soc. Exper. Biol. & Med.* 30: 1210, 1933.
17. Idem: Ueber krystallisiertes Harn-Urobilin, sowie weiteres über Stercobilin und Kopromesobiliviolin, *Ztschr. f. physiol. Chem.* 221: 145-155, 1933.
18. Idem: A Comparison of Natural Crystalline Urobilin (Stercobilin) With That Obtained in Vitro From Mesobilirubinogen, *Proc. Soc. Exper. Biol. & Med.* 32: 1508, 1935.
19. Idem: Ueber krystallisiertes Stercobilin bzw. Urobilin, *Ztschr. f. physiol. Chem.* 233: 39-58, 1935.
20. Siedel, W., and Meier, E.: Synthese des Urobilins (Urobilin IX a) sowie der isomeren Urobiline- III a and XIII a, *Ztschr. f. physiol. Chem.* 242: 101-132, 1936.
21. Watson, C. J., and Schwartz, S.: Nature of Urobilin Obtained After Amalgam Reduction of Human Fistula Bile, *Proc. Soc. Exper. Biol. & Med.* 49: 636-640, 1942.
22. Watson, C. J., Sborov, V., and Schwartz, S.: Formation of Laevo-rotatory Stercobilin From Mesobilirubinogen in Human Feces, *Proc. Soc. Exper. Biol. & Med.* 49: 647-651, 1942.
23. Schwartz, S., and Watson, C. J.: Isolation of a Dextro-rotatory Urobilin From Human Fistula Bile, *Proc. Soc. Exper. Biol. & Med.* 49: 641-643, 1942.
24. Schwartz, S., Sborov, V., and Watson, C. J.: Formation of d-urobilin From Mesobilirubinogen in Human Bile, *Proc. Soc. Exper. Biol. & Med.* 49: 643-647, 1942.
25. Watson, C. J.: Studies of Urobilinogen; an Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces, *Am. J. Clin. Path.* 6: 458-475, 1936.
26. Watson, C. J.: The Bile Pigments, *New England J. Med.* 227: 663-672, 705-711, 1942.

# ACUTE PHYSIOLOGIC RESPONSES IN EXPERIMENTAL HEAD INJURY WITH SPECIAL REFERENCE TO THE MECHANISM OF DEATH SOON AFTER TRAUMA

E. S. GURDJIAN, M.D., DETROIT, MICH., AND MAJOR JOHN E. WEBSTER,  
MEDICAL CORPS, U. S. ARMY

*(From the Department of Surgery, Wayne University College of Medicine, and  
Department of Neurosurgery, Grace Hospital)*

IN TWO previous communications,<sup>12, 19</sup> the subject of experimental head injury was discussed and the salient points concerning vital functions were brought out. In this report are considered in greater detail the changes of blood pressure, pulse, respiration, the conscious state, and reflexes in acute trauma. The mechanism of death soon after trauma will be analyzed. The changes to be described are seen immediately following the trauma and should not be confused with the manifestations of vital functions in more chronic forms.

## METHODS AND MATERIALS

Mongrel dogs, weighing between 7 and 15 kg., were used for these experiments. Morphine analgesia was used in quantities of 20 mg. per kilogram of body weight. The drug was administered subcutaneously. When operative procedures were necessary, intravenous nembutal anesthesia was used. The exposure of vessels was done under  $\frac{1}{2}$  of 1 per cent procaine infiltration anesthesia.

The blood pressure was recorded from the femoral artery, respirations by means of a balloon about the thorax. The cranial trauma was administered by means of a hammer, falling weight, striking object propelled by a spring pendulum, and by shooting. Except in the case of the hammer, the velocity and the force of the striking object were controlled. The head injury was delivered after exposure of the bone by reflection of the scalp and the underlying masseter muscles.

A number of preparations were made prior to injury. In two animals the spinal cord was sectioned at the first thoracic segment twenty-four hours before the injury was delivered. In three animals the adrenal glands were removed before injury. In five animals the vagus nerves were cut and the carotid arteries ligated and sectioned. In three animals yohimbine was administered intravenously in order to remove the influence of the sympathetic nervous system by chemical means. After the administration of the drug, if intravenous adrenalin did not in-



fluence the blood pressure, the animal was thought to be well yohimbized. In three animals, bilateral supratentorial exposure of brain was made before injury by bullet. In nine dogs correlations were made between changes in medullary function and the electroencephalographic findings. The animals were prepared by first inserting electrodes in both parietal regions on either side of the midline. Before, during, and after trauma, an attempt was made to record the electrical activity of the brain.

#### ACUTE PHYSIOLOGICAL RESPONSES

Irrespective of the method of injury, the acute responses are divisible into three types: (1) minimal, (2) moderate, and (3) profound. In the group with minimal response, there was, as a rule, no change in blood pressure, pulse, or respiration. The blood pressure rarely showed an increase at the time of the blow. In this group the lid reflexes were normal and the animal was in excellent condition; his chances of survival were excellent. However, in one instance there was hypertension with respiratory pause in a conscious animal and in another only hypertension occurred, with normal respirations and normal conscious state.

Among the animals with moderate response, there was a short period of unconsciousness, evidenced by inability to respond to painful stimuli. Hypertension usually occurred immediately following the blow. This lasted 60 to 120 seconds. There was an associated tachycardia which usually disappeared within 40 to 80 seconds. In an occasional case vagal stimulation, as evidenced by decreased pulse rate and subsequent escape, occurred. The respirations were very rarely increased (Fig. 1), indeed, an apnea usually occurred which lasted from 10 to 40 seconds with later return to normal. The majority of these animals would survive the injury. The corneal reflex was lost usually for several seconds. In a few instances, the animal became unresponsive to pain without loss of reflexes. In one example, the blood pressure dropped immediately following trauma and eventually became restored to its original level. Respirations which had stopped for 70 seconds were resumed (Fig. 2).

Among those animals with profound effect, the picture was typical in almost every instance. The animal was unconscious. There was a sudden sharp rise in blood pressure at the instant of trauma averaging between 75 and 125 mm. of mercury (Fig. 3). Slowly the blood pressure dropped, in many instances to zero at the end of 3 to 6 minutes. In Fig. 2, a secondary rise interrupting the steep blood pressure fall is attributable to medullary anemia. In a few cases, after an initial drop, a new increase in pressure appeared, associated with renewed respirations. But eventually, even though there were spontaneous respirations, the blood pressure failed and death ensued. In one instance, a profound effect obtained without increase in the pressure. In another

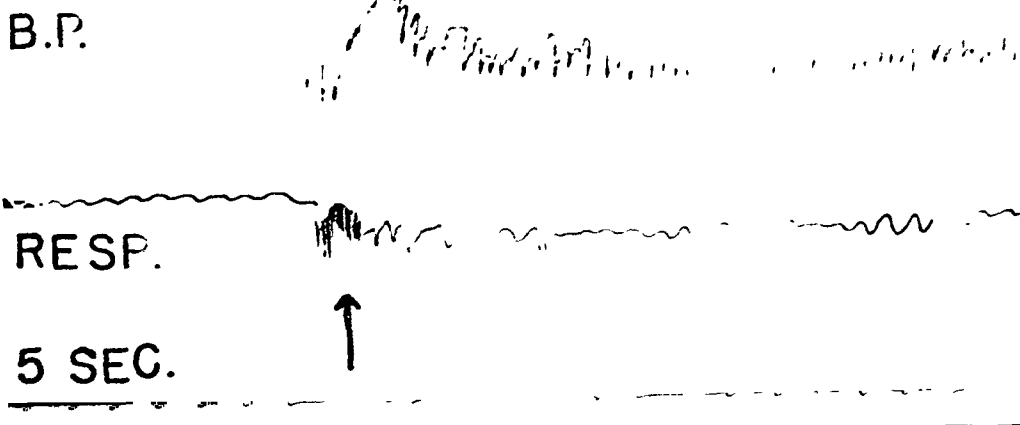


Fig. 1.—An example of increased respirations and vasomotor activity with lost corneal reflexes. Dog 39 was administered a single hammer blow to the right parieto-occipital region of the head. Corneal reflexes were lost for 29 seconds. There was a steep rise of blood pressure and stimulation of respirations lasting 7 seconds. The dog had no fracture of the skull. There were contusions of the base with moderate hemorrhage. It would have survived the injury.

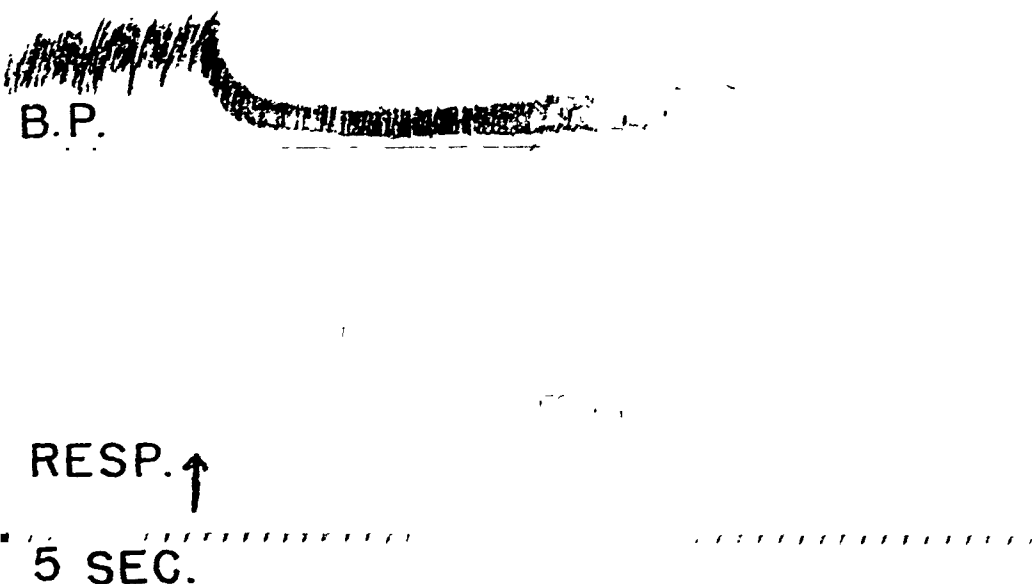


Fig. 2.—An example of a drop in blood pressure in a moderately injured dog. Dog 158 was injured with the pendulum. There was a drop in blood pressure with bradycardia. The blood pressure slowly rose to its original level with the animal carrying on satisfactorily. Respirations became regular at the end of 70 seconds. A large area of depression with extrusion of the brain was obtained. There was severe laceration of the left parieto-occipital cerebrum and the superior surface of the cerebellum. Cross sections of the brain stem and spinal cord revealed many areas of punctate hemorrhage. In the spinal cord there was a large, 2 mm. hemorrhage about the central canal. Small punctate hemorrhages were also present.

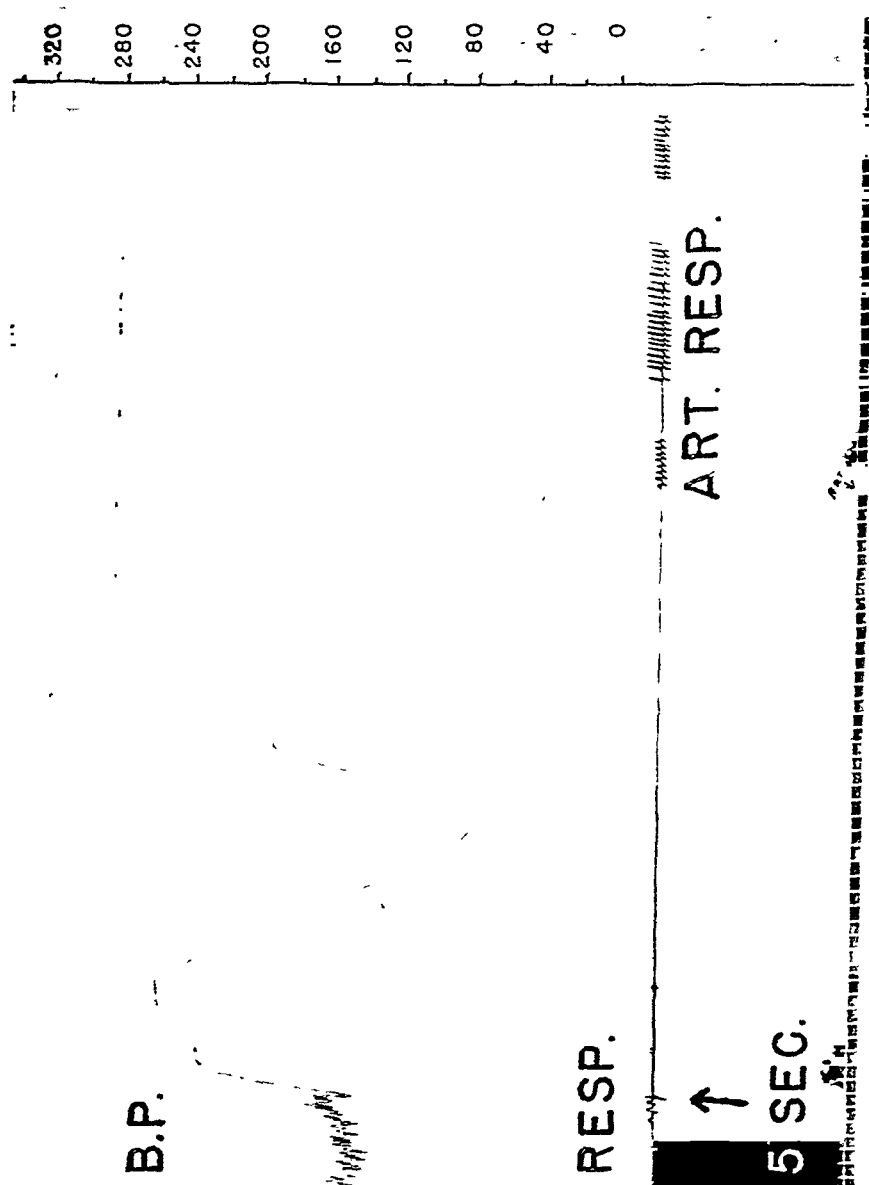


Fig. 3.—An example of profound effect characterized by pressor response, respiratory paralysis, initial spasticity with neck retraction followed by stilling within two minutes. Note the initial steep rise of blood pressure (110 mm. Hg) followed by a steep fall. The fall is interrupted by a secondary rise in pressure, most probably due to medullary anoxia. Artificial respirations were at no avail. This animal had been hit upon the head the day previously, with a moderate response. This record was obtained after a blow to the left occipitoparietal region.

case, the blood pressure dropped with complete failure. The pulse increased remarkably with the blow, and this increase was sustained to the end. In a few instances there was vagal inhibition followed shortly by escape. The respirations invariably stopped and in some cases there was sufficient recovery for spontaneous respiratory movements followed by failure. All animals in the profound group either died within a few minutes after the beginning of the experiment or within an hour or two if not sacrificed. Associated with changes in the vital functions there was almost always a lost corneal reflex. In some animals the corneal reflex returned to disappear again in a short time. However, in one example, a profound effect was obtained and yet reflexes were active almost to the last. In the moderately and severely injured animals generalized rigidity with extension of limbs and retraction of the head and neck was seen frequently, followed by limpness within a short time.

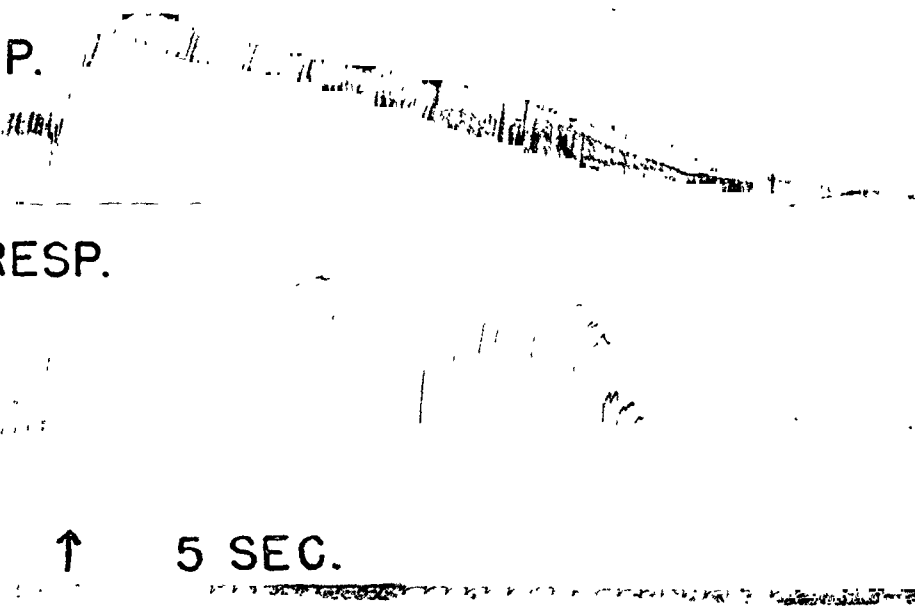


Fig. 4.—An example of head injury in an adrenalectomized animal. In Dog 175 both adrenal glands were removed under nembutal anesthesia. The corneal reflexes were present before injury. A right parieto-occipital hammer blow caused a profound pressor effect (100 mm. Hg) with loss of respirations for 40 seconds. They returned for 120 seconds, followed by final loss and death of the animal. There was marked tachycardia and a steep fall of blood pressure following the initial rise.

*Section of Both Vagi and Carotid Arteries.*—A section of both vagi caused a marked increase in the pulse rate associated with a moderate increase in the blood pressure which became normal again within  $\frac{1}{2}$  to 1 hour. In the group of animals in which the vagi and the carotid arteries were sectioned, injury to the head caused responses similar to those seen in the intact animal except that there was no change in the pulse rate.

*Adrenal Influence.*—These animals were prepared twenty-four hours previously by removal of both adrenal glands under nembutal anesthesia. The head injury was administered under morphine analgesia. The injury in this group caused the usual rise in the blood pressure associated with respiratory failure (Fig. 4). It was believed that the increase in blood pressure in this group of head injury experiments was not mediated by a humoral factor (adrenalin liberation).

*Sympathetic Influence.*—Several animals were prepared twenty-four hours previously by section of the spinal cord at the level of the lower cervical segment under nembutal anesthesia. The injuries were administered under morphine analgesia (Fig. 5). These animals had a low blood pressure following the spinal cord section. Several blows to the head with eventual profound effect were never associated with hypertension. It seems reasonable to assume that if the spinal cord had been intact, there would have been the usual acute hypertension ordinarily associated with trauma.

B. P.



R. SP.

5 SEC.

Fig. 5.—An example of head injury after section of lower cervical spinal cord. Dog 180 was prepared by section of the spinal cord at the lower cervical level under nembutal anesthesia. He was allowed to recover overnight, and on the following day hammer blows were administered on the right parieto-occipital skull under morphine analgesia. The accompanying figure shows the aftereffects of the fourth blow. A compound fracture with lacerations and contusions of the brain was produced with hemorrhage at the base. The reflexes and respirations were lost immediately. Respirations returned in 90 seconds and disappeared again 70 seconds later. At one point there was a marked vagal effect. The animal died.

The use of yohimbine as a sympathetic paralyzing agent was instructive (Fig. 6). When the animal was given a sufficient amount of yohimbine and when its blood pressure could not be raised by injection of  $\frac{3}{4}$  c.c. of adrenalin solution, injury to the head was never associated with increase in blood pressure. These two groups of experiments suggest that the sympathetic nervous system mediates the acute peripheral hypertension in head injury.

*Head Injury After Bilateral Craniotomy and Exposed Brain.*—In several animals the cranial cavity was opened on both sides. The dura was incised and reflected to expose the brain. Under these conditions

a supratentorial bullet wound never caused a pressor effect even though three out of four animals were mortally wounded. In each instance there was marked laceration and dissolution of brain tissue. The respirations were lost in two instances with no return. In one there was no loss of respirations, and in another they waxed and waned on several occasions.

The lack of a pressor effect in these experiments is another argument proving that the increase in the blood pressure is brought about by medullary stimulation and could not be caused by stimulation of supratentorial cortical or subcortical centers. This was also proved beyond doubt by Polis<sup>17</sup> and Denny-Brown and Russell<sup>18</sup> in decerebrate preparations. In such animals, the pressor effect was obtained after adequate blows to the head even though connections with higher centers were disrupted.

B.P.

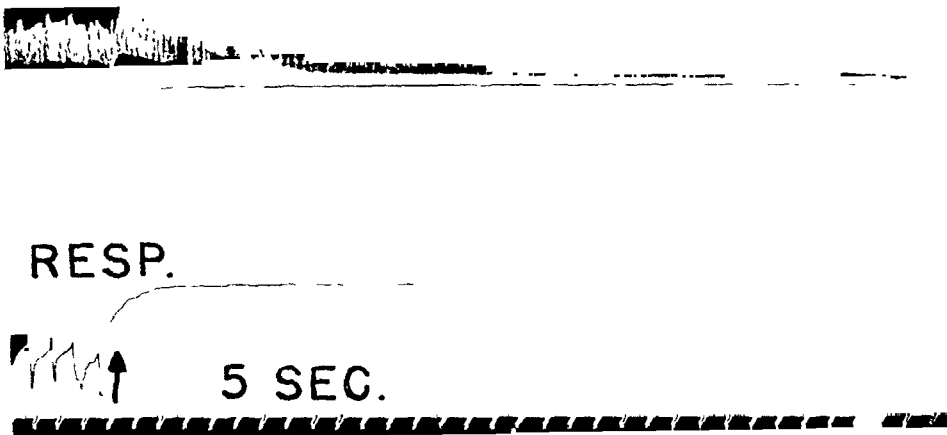


Fig. 6.—Yohimbine experiment. Dog 181 was given 2 c.c. of yohimbine, intravenously (1 per cent solution) to abolish the sympathetic nervous system response. The blood pressure fell, but the heart rate remained about the same. Ten minutes later another cubic centimeter of yohimbine was given. Three minutes afterward  $\frac{3}{4}$  c.c. of 1 to 1,000 adrenalin solution injected intravenously caused tachycardia, but no change in blood pressure. It was now assumed that the dog's sympathetic nervous system was well neutralized. The dog was hit a heavy blow over the occiput. There was no change of reflexes or respirations, or rise of blood pressure. The dog was struck a second time with profound effect. Reflexes and respirations were abolished. There was no rise in blood pressure and it fell to zero within a few minutes.

*Effects of Injury of Medulla and Upper Spinal Cord on Vasomotor and Respiratory Centers.*—In four animals the medulla or spinal cord was injured by gunshot. In two instances injury was at the obex, in one 5 mm. below the obex, and in another 5 cm. down the spinal cord. In the two dogs where the neighborhood of the obex was destroyed by a .22 caliber bullet, the pressor effect did not appear (Fig. 7). In the animal with injury a little below the obex, there was a marked pressor response

(Fig. 8). In the fourth animal with injury lower down the cervical spinal cord, there was no change in the systolic blood pressure but the pulse pressure increased markedly (Fig. 9).

These results differ from those obtained by Polis,<sup>17</sup> who stated that injury to the vasomotor centers or the cervical spinal cord uniformly causes hypertension. The dissolution of the vasomotor centers by injury should, theoretically at least, cause no pressor response, whereas a lesion lower down or higher up may stimulate the center as in other forms of head injury.

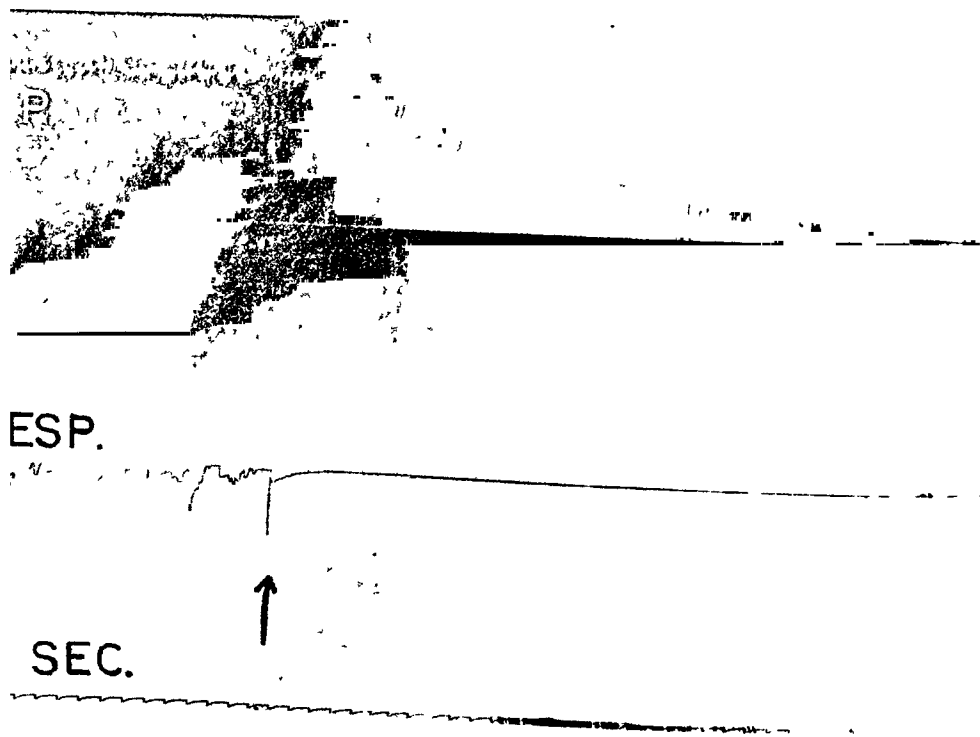


Fig. 7.—An example of a bullet wound of the vasoconstrictor center with no initial pressor response. In order to injure the medulla more accurately, Dog 108 was preprocaine infiltration. The closed-cavity hydrodynamics of the head were not disturbed. The medulla was then shot with a 22 caliber bullet, with profound effect but no rise in blood pressure. There was cessation of respirations and loss of corneal and lid reflexes. Autopsy revealed an injury in the neighborhood of the obex.

*Electroencephalographic Correlations.*—A study was made of the changes in the electrical activity of the cortex at the time that evidences of medullary involvement were present. In a number of the animals with profound effect and lost corneal reflexes the electrical activity of the cortex in the parietal region continued unaltered. In others the activity of the cortical surface became impaired with little or no change in medullary functions. It was felt that in the latter group a more direct injury to the cortex was brought about by the trauma and a consideration of the former suggested that a blow to the head might be

severe enough to cause medullary involvement without at the same time upsetting the electrical activity of the surface of the brain. In most experiments recording of the brain waves was resumed within 3 to 6 seconds after the blow and even though the changes during this period are unknown, the evidence points to selective involvement of the nervous system. That is, in some animals or at certain times in the same animal, there was greater involvement of medullary centers than of the cortex. In other animals, and at times in the same preparation, the medullary centers were spared and there was marked involvement of the cortex (Figs. 10 and 11).

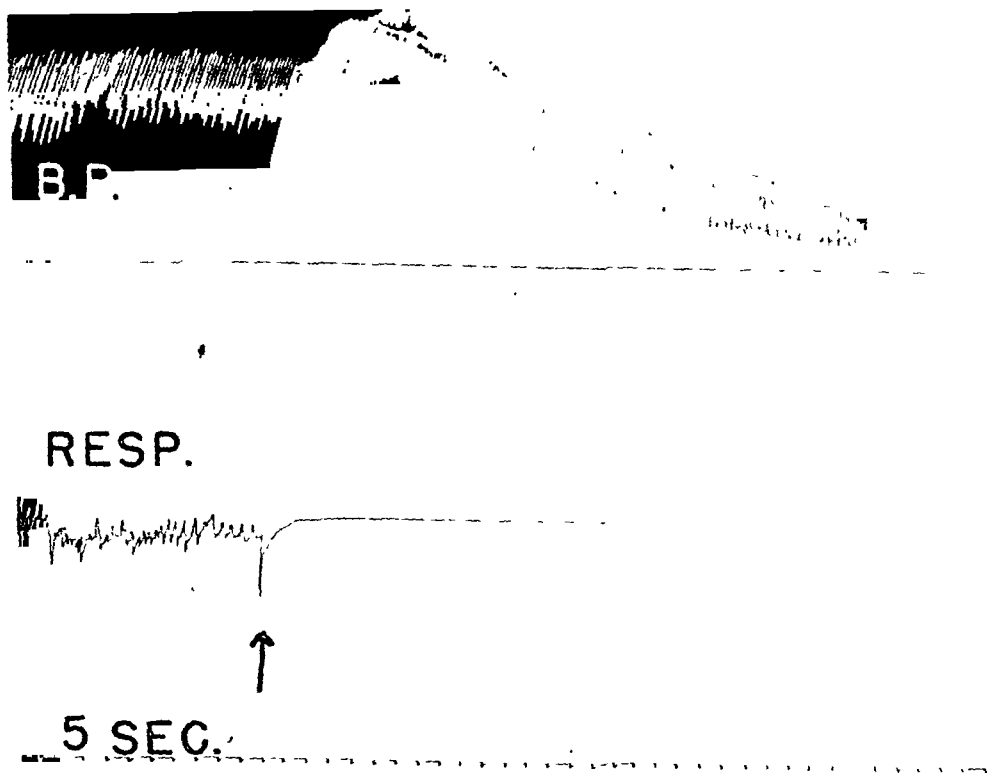


Fig. 8.—An example of injury of the spinal cord a few millimeters below the obex with a pressor effect. Dog 103 was injured by shooting at the neck with a .22 bullet in an attempt to injure the medulla. A remarkable rise of blood pressure with tachycardia and progressive failure associated with lost respirations and reflexes were obtained. Autopsy revealed that the bullet had entered a fingerbreadth below the obex. There were bruises and contusions of the frontal lobes suggesting transmitted energy throughout the closed skull cavity.

In Fig. 10, the electroencephalographic findings following a single fatal blow are shown. It can be noted that 9 per cent frequency changed following the head injury to 24 per second frequency with a rather definite spiky character. Over a period of 6 minutes the record showed decreasing voltage but the frequency was sustained almost to the last; eventually only faint vertical sweeps were noted as the animal died. The



simultaneous recording of the corneal reflexes revealed a loss immediately after the trauma with return in 40 seconds. For the ensuing 90 seconds, corneal reflexes could be obtained. After that they were lost while evidences of cortical electrical activity were still present.

A different type of record is noted in Fig. 11. After blow number one, there is delta activity and during this period the eye reflexes were gone. In 2 minutes there was return of reflexes and a more normal electrical activity although some delta pattern is still present. Just after the second blow, the electrical activity of the brain did not change but its amplitude and voltage continued to decrease until a straight line record was being obtained. During part of this seeming inactivity of the cortex, the reflexes and respirations were still present to disappear again just before cessation of all activities.

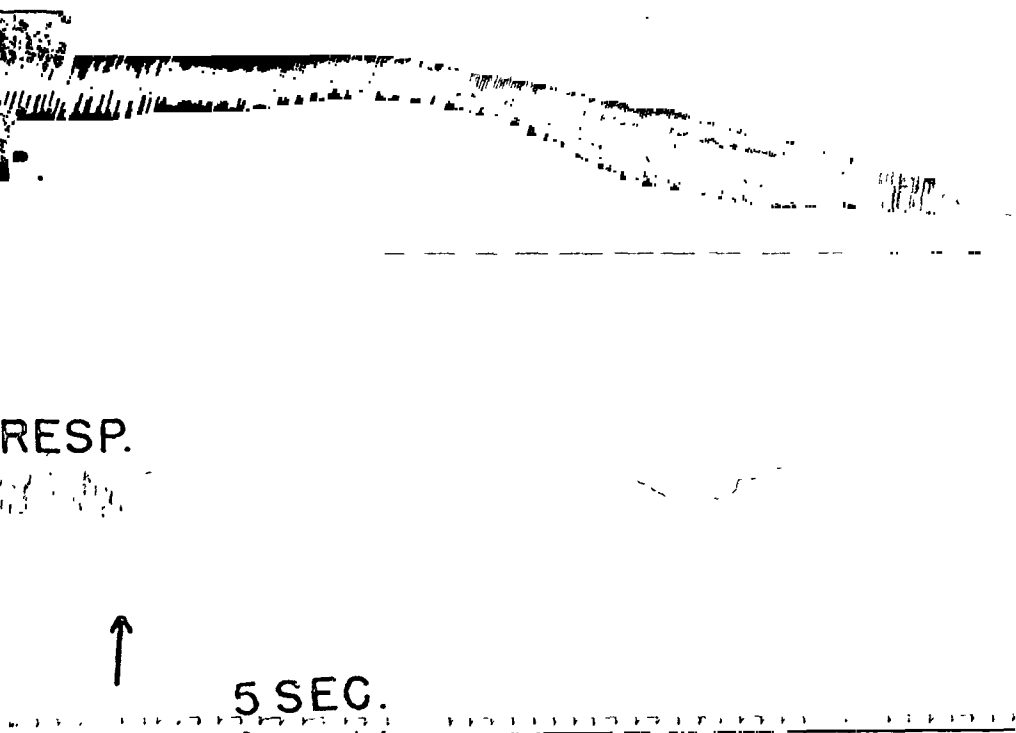


Fig. 9.—A spinal cord injury with profound effect and no rise in blood pressure. In Dog 110, a bullet wound of the spinal cord 5 cm. below the medulla resulted in rapid failure with no initial pressor effect. Apnea ensued and after 30 seconds the reflexes were lost. Examination revealed bruises and contusions of the frontal lobes. The closed-cavity hydrodynamics apparently were operative even at this low level (5 cm. below the medulla). The marked increase in the pulse pressure suggests vasoconstrictor paralysis with consequent loss of vascular-bed tone.

#### CONCLUSIONS

Experimental head trauma has been studied in great detail by Cannon,<sup>1</sup> Denny-Brown and Russell,<sup>3</sup> Duret,<sup>4</sup> Fischer,<sup>6</sup> Kocher,<sup>15</sup> Miller,<sup>16</sup> Polis,<sup>17</sup> Scott,<sup>18</sup> and others. For the purposes of the present discussion, the material presented by Polis in 1894 and that presented by

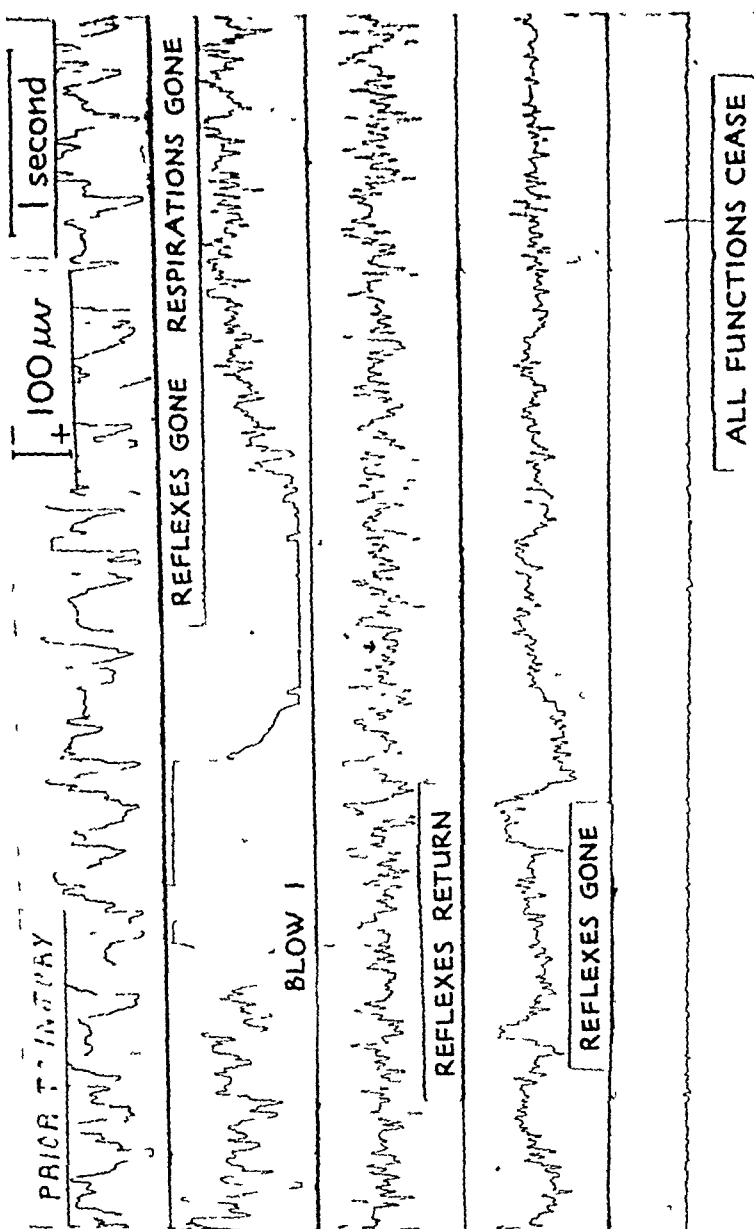


Fig 10.

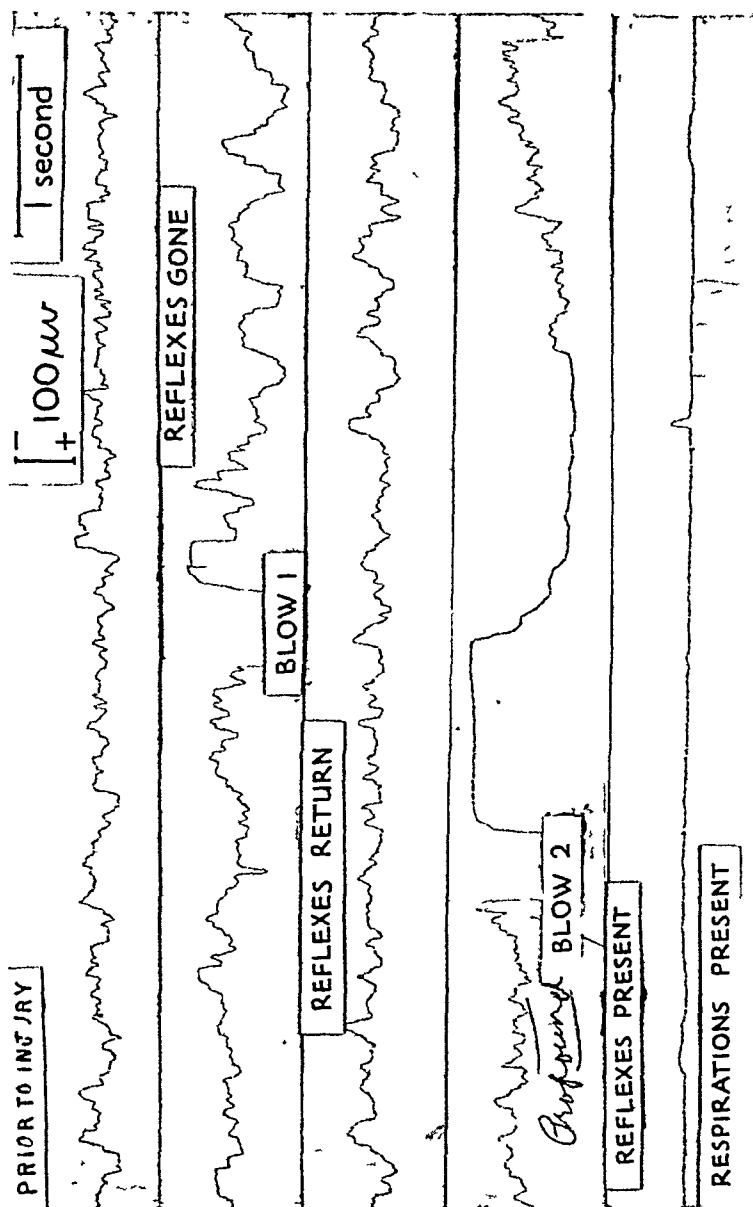


Fig 11

Denny-Brown and Russell in 1941 are the most pertinent. The work of Polis is particularly commendable. Fifty years ago he recorded his findings in experimental head injury, including gunshot wounds, and his results with a few exceptions are acceptable at the present time. Polis worked with normal and decerebrate animals. He concluded that death from head injury results from vasomotor failure after an initial increased activity, and respiratory paralysis. He felt that in moderate injuries there was a constriction of intracranial blood vessels and that in severe injuries there was a vasodilatation. Polis described medullary paralysis without lesions, suggesting that death from concussion is through medullary paralysis. Denny-Brown and Russell have reaffirmed most of the findings of Polis. They re-emphasized the fact that in trauma to the head, medullary centers may become paralyzed with or without visible lesions in the brain stem and medulla. According to these authors, in severe trauma there is a cerebral vasodilatation, with blood pressure failure due to vagus stimulation which counteracts the pressor effect of the vasomotor center injury, eventuating in the death of the animal.

In the present study, changes in blood pressure, pulse, and respirations were carefully scrutinized in the light of associated changes in the conscious state and reflexes in dogs with morphine analgesia. Under this form of analgesia the ability to respond to painful stimulation by forceps or dynamometer was considered a sign of adequate conscious state. Lack of response to pain was seen without loss of corneal reflexes or after the reflexes had returned following an initial loss. In some animals evidences of medullary involvement coexisted with normal response to pain. Unconsciousness was always present when the corneal reflexes were lost. It was felt that involvement of the medullary ocular reflex centers by trauma represented a more severe evidence of injury than unconsciousness. The reflex of deglutition was preserved during unconsciousness but hopping reflexes were lost.

The vasomotor center was stimulated by an adequate energy, and the increase in blood pressure immediately following trauma was the most common finding in moderately and profoundly injured dogs. The exceptions to this rule were: First, when the vasomotor center was destroyed, under such circumstances there was no increase in pressure and circulatory failure occurred within a few minutes. Second, in a certain number of supratentorial blows with extensive depression of bone and laceration of brain tissue, no change or drop in pressure occurred immediately following the trauma. The mechanism of a drop in pressure following the head trauma has been described as a vagal effect by Denny-Brown and Russell,<sup>3</sup> and they state that such vagal effects are never seen except in subconcussive blows. In our experience, a drop in blood pressure may occur also in a seriously injured animal with eventual complete circulatory failure.

A vasoconstrictor mechanism rather than a humoral discharge causes the hypertension since adrenalectomized animals showed the usual pressor response following trauma, while the animals with section of the cervical spinal cord, and those which were adequately yohimbized, did not. This has also been shown in Cushing<sup>2</sup> preparations by Freeman and Jeffers.<sup>10</sup> They found that sympathectomized animals did not have a pressor response on increase of the intracranial pressure by forcing saline solution into the cisterna magna. They further noted that if only the upper four thoracic sympathetic ganglia and both vagi were sectioned (denervated heart), no pressor response occurred.

In very seriously injured animals where the pressor response is followed by circulatory failure, the reason for the initial vasomotor stimulation may seem difficult to understand. Why doesn't failure occur at once? There is failure at once if the injury causes dissolution of the vasomotor center, as is shown in some of the accompanying experiments. But if the vasomotor center is allowed to remain intact, with energies acting upon it from a distance, its first discharge is, almost always, one of a peripheral vasoconstriction with consequent increase of the blood pressure. This is a protective mechanism for it helps to insure the blood supply to the brain stem and it occurs even though the vasomotor center may have been irreparably injured. The complete destruction of the neighborhood of the obex is uniformly followed by circulatory failure with no initial pressor response. In other words, a dissolution of the center itself causes the death of the animal. This is an important point. The work of Forbes and Wolff<sup>9</sup> has shown that stimulation of the central stump of the cut vagus causes a fall in blood pressure as well as pial vascular dilatation. It is conceivable that a depressor mechanism may be the cause of a drop in pressure in some experiments, but a paralysis of the vasomotor center itself is usually the cause of the circulatory failure and death.

While a peripheral vasoconstriction is proved beyond doubt, what is the simultaneous status of vessels in the cranial cavity? Are they constricted like the peripheral vessels? Polis<sup>11</sup> fifty years ago thought that in moderately injured dogs there was a constriction of intracranial blood vessels and in severely injured dogs there was a vasodilatation. Some of his conclusions were based on the bleeding time from the cut jugular vein. Denny-Brown and Russell<sup>3</sup> repeated these experiments. They noted the amount of bleeding from the jugular vein was definitely increased immediately after a severe trauma. They have concluded that this may represent a central vasodilatation. The work of Finesinger and Putnam,<sup>7</sup> Fog,<sup>7</sup> Forbes, Nason, and Wortman,<sup>8</sup> Gellhorn,<sup>11</sup> and others shows that the peripheral and the central blood vessels may simultaneously be in a dissimilar state of tone. With peripheral vasoconstriction due to a drop in blood pressure there is intracranial vasodilatation to insure adequate blood supply to the brain. Thus, the

presence of central vasodilatation with peripheral vasoconstriction may be the expected phenomenon and need not necessarily be construed as an evidence of traumatic stimulation of a depressor mechanism, since it may happen with any other factor causing peripheral vasoconstriction.

The evidence seems to indicate that an injury of sufficient severity to cause a paralysis of the vasoconstrictor center causes death mainly through this paralysis. The failure of the blood pressure is in fact due to the failure of the center. The stimulation of vagoglossopharyngeal centers need not be the cause of the fatal drop in blood pressure.

Respirations were affected in a multitude of ways. In the group with minor trauma usually there was no change in respirations. Occasionally stimulation associated with a slight increase in blood pressure was noted. There was apnea of varying periods in the group with moderate injuries; the respirations usually reappeared within 60 seconds. In the group with profound injuries there was respiratory paralysis with no spontaneous return in some animals or after the initial respiratory paralysis there was return for a short while with final failure and death of the animal.

Respiratory paralysis is a direct result of injury to the respiratory center. The respiratory center or the vasomotor center or both may be affected by trauma. At times the reappearance of an occasional respiratory movement has a tendency to revivify the animal with an increase in blood pressure. In the severely injured animal the vasomotor mechanism fails in spite of artificial respirations.

The pulse almost always increased following trauma. In animals with intact vagi there was an occasional vagal stimulation with bradycardia with escape from the inhibition. In one of the experiments in which the animal was decompressed bilaterally and shot with a .22 rifle, the vagal influence remained throughout, following the injury. Evidence of vagal stimulation was noted in some seriously injured dogs.

The electroencephalographic changes immediately following trauma to the head did not correlate with the medullary involvement. In some seriously injured dogs with paralysis of respirations, vasomotor mechanism, and lost corneal reflexes, the electrical activity of the brain from the parietal region continued until just before death of the animal. In others, the electrical activity of the brain failed in the presence of respirations and corneal reflexes. Obviously an injury in the neighborhood of the electrodes may be associated with cortical electrical changes transmitted through it. But in these preparations, care was taken to deliver the blow at a reasonable distance from the electrodes. Under these circumstances evidences of medullary paralysis could be obtained without a simultaneous inactivity of the brain waves.

In the human being, death soon after cranial trauma is common. In a previous report in the JOURNAL,<sup>13</sup> 61 of 151 consecutive autopsies were on patients dead on admission to the hospital or found dead

at the scene of the accident. In 19, there were punctate hemorrhages in the medulla and pons with little or no other associated intracranial lesions to explain the death. In this group it is very likely that death was due to medullary paralysis, and comparison of a typical pathologic picture in a fatal animal experiment with human autopsy reveals many similarities in type and distribution of lesions. (Fig. 12). Although there are no adequate human studies of clinical behavior immediately following trauma, it seems reasonable to suspect that the mechanism of death soon after injury in the human being is essentially the same as in the experimental animal.

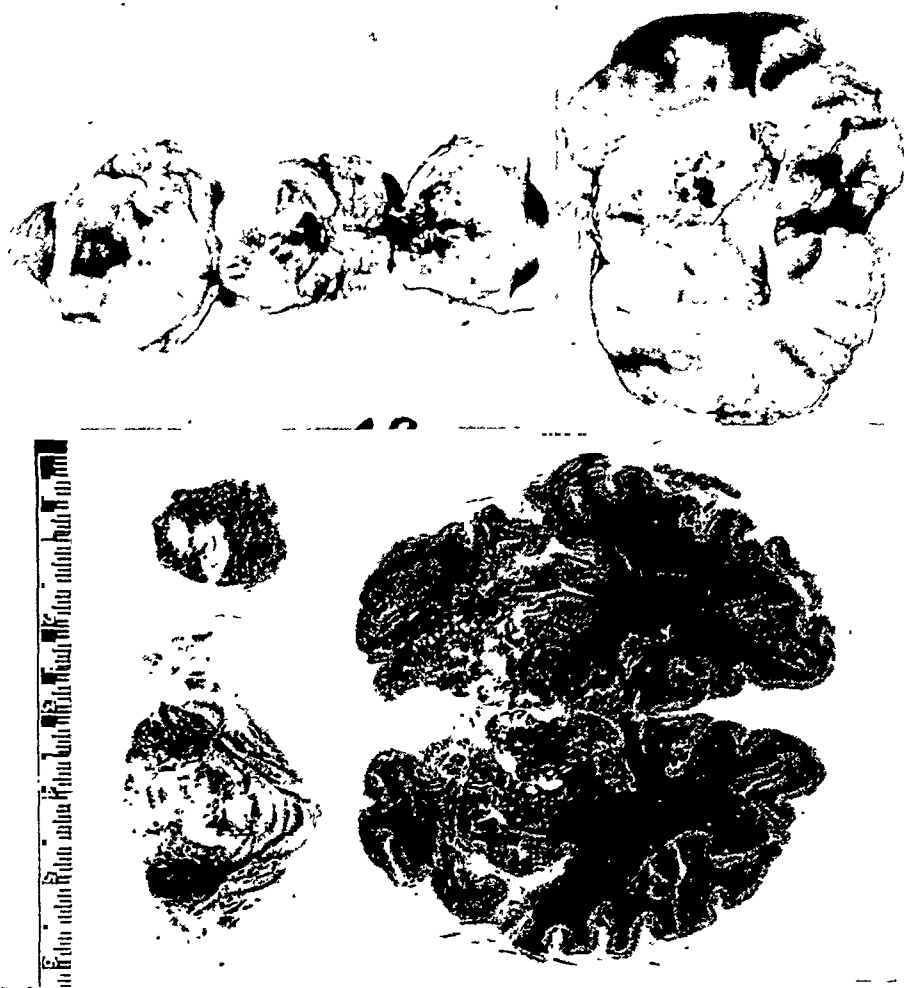


Fig. 12.—To the left, section of the brain of the dog with punctate hemorrhages in thalamus and brain stem. The animal died as a result of medullary paralysis, following a parieto-occipital head injury. To the right, section of the brain of a human being found dead at the scene of the accident. Punctate hemorrhages of the posterior thalamus and brain stem are noted. Observe the similarity of the distribution of lesions.

## SUMMARY

1. The acute physiologic responses to injury may be minimal, moderate, or profound. In moderate and profound injuries usually there is a sudden increase in blood pressure with respiratory loss, unconsciousness (no reaction to painful stimuli), loss of palpebral and corneal reflexes, and frequent generalized rigidity followed by limpness. In moderate injuries the animal survived or died, in the group with profound injuries death was almost invariable.

2. Under morphine analgesia the ability to respond to pain was considered an adequate sign of consciousness. In some animals vasoconstrictor stimulation and respiratory pause coexisted with normal response to pain.

3. Loss of corneal reflexes represents a more profound response to injury than unconsciousness. Some animals were frequently observed to be unconscious with active palpebral and corneal reflexes.

4. The acute changes in blood pressure, respirations, and reflexes following trauma to the head are due to stimulation or paralysis of medullary centers.

5. The acute hypertension following trauma is caused by peripheral vasoconstriction as shown in experiments on adrenalectomized and yohimbinized animals and those in which the lower cervical spinal cord was sectioned. A drop in blood pressure following trauma was seen in some experiments. Dissolution of the vasomotor center by .22 rifle caused failure without an initial pressor response.

6. Respiratory paralysis is a common manifestation in severely injured dogs. However, in some with pressor response there was little or no change in respirations and in others with respiratory paralysis there was little or no change in vasomotor activity. Increase in respiratory rhythm associated with other evidences of medullary stimulation was possible but infrequent.

7. Evidences of vagal paralysis were common in most of the moderately and severely injured animals. Vagal stimulation with bradycardia was seen in some moderately and severely injured dogs.

8. The depressor centers mediated through the vagoglossopharyngeal complex may have been stimulated to cause a drop in blood pressure in some experiments but it is felt that the vasomotor failure is mainly due to a failure of the vasomotor center in the medulla.

9. Electroencephalographic studies of the cortex with simultaneously observed evidences of medullary paralysis reveal that the cortical activity may be unhampered even though the medulla is badly damaged and vice versa.

10. In the experimental animal, death from acute trauma was due to paralysis of the vasomotor center.



## REFERENCES

1. Cannon, W. B.: Cerebral Pressure Following Trauma, *Am. J. Physiol.* 6: 91-121, 1902.
2. Cushing, H.: Concerning a Definite Regulatory Mechanism of the Vasomotor Centre Which Controls Blood Pressure During Cerebral Compression, *Bull. Johns Hopkins Hosp.* 12: 290, 1901.
3. Denny-Brown, D., and Russell, W.: Experimental Cerebral Concussion, *Brain* 64: 93-164, 1941.
4. Duret, H.: *Etudes experimentales sur les traumatismes cerebraux*, Paris, Thèse de Paris, No. 63, 1878.
5. Finesinger, J. E., and Putnam, T. J.: Cerebral Circulation XXIII, Induced Variations in Volume Flow Through the Brain Perfused at Constant Pressure, *Arch. Neurol. & Psychiat.* 30: 775-794, 1933.
6. Fischer, H.: Ueber die Commotio cerebri—Volkman's Sammlung, *Klin. Vortr.* 1871, Series 1, No. 27, p. 119.
7. Fog, M.: Cerebral Circulation. The Reaction of the Pial Arteries to a Fall in Blood Pressure, *Arch. Neurol. & Psychiat.* 37: 351, 1937; The Relationship Between the Blood Pressure and the Tonic Regulation of the Pial Arteries, *J. Neurol. & Psychiat.* 1: 187-197, 1938.
8. Forbes, H. S., Nason, G. I., and Wortman, R. C.: Cerebral Circulation XLIV. Vasodilation in the Pia Following Stimulation of the Vagus, Aortic and Carotid Sinus Nerves, *Arch. Neurol. & Psychiat.* 37: 334-350, 1937.
9. Forbes, H. S., and Wolff, H. G.: Cerebral Circulation, *Arch. Neurol. & Psychiat.* 19: 1057-1086, 1928.
10. Freeman, N. E., and Jeffers, W. A.: Effect of Progressive Sympathectomy on Hypertension Produced by Increased Intracranial Pressure, *Am. J. Physiol.* 128: 662-271, 1940.
11. Gellhorn, Ernest: *Autonomic Regulations*, New York, 1943, Interscience Publications, Inc.
12. Gurdjian, E. S., and Webster, J. E.: Experimental Head Injury With Special Reference to the Mechanical Factors in Acute Trauma, *Surg., Gynec. & Obst.* 76: 623-634, 1943.
13. Gurdjian, E. S., Webster, J. E., and Arnkoff, H.: Acute Craniocerebral Trauma, *SURGERY* 13: 333-353, 1943.
14. Koch, W., and Filehne, W.: Beiträge zur experimentellen chirurgie, *Arch. f. klin. Chir.* 17: 190-231, 1874.
15. Kocher, T.: *Nothnagel Specielle Pathologie und Therapie*, vol. 5, Vienna, 1901, A. Holder.
16. Miller, G. G.: Cerebral Concussion, *Arch. Surg.* 14: 891-916, 1927.
17. Polis, A.: *Recherches experimentales sur la commotion cérébrale*, *Rev. de chir.*, Paris 14: 274-319, 645-730, 1894.
18. Scott, W. W.: Physiology of Concussion, *Arch. Neurol. & Psychiat.* 43: 270-283, 1940.
19. Webster, J. E., and Gurdjian, E. S.: Acute Physiological Effects of Gunshot and Other Penetrating Wounds of the Brain, *J. Neurophysiol.* 6: 255-262, 1943.

## THE EFFECT OF POSITION ON SHOCK PRODUCED BY HEMORRHAGE

ALFRED LARGE, M.D., St. Louis, Mo.

*(From the Department of Surgery, Washington University School of Medicine)*

ACCUMULATED experimental evidence forms a concrete basis for our present conception of many of the changes occurring in shock, from whatever cause. Thus, most of the measures used clinically in the prevention and treatment of shock have an accepted physiologic basis. The so-called shock position is probably an exception to this rule, for although elevation of the foot of the bed seems to be universally regarded as the proper position for the patient in shock (provided, of course, that chest or head injuries do not exist), there is, as far as I am aware, no experimental evidence to support such a maneuver.

### METHOD

Medium-sized mongrel dogs weighing 6 to 12 kg. were used as experimental animals. They were allowed to have water but no food for a period of eighteen hours prior to the experiment. Each animal was tied flat on its back on an animal board; the boards were then tilted so that one group of dogs had the head raised with the long axis of the body 30 degrees from the horizontal, while the other had the head lowered to a similar degree, and this position was maintained for the duration of the experiment. Thirty-two dogs were used, sixteen in each of the designated positions. Two or four dogs were bled at a time, and an effort was made to use animals as much alike in weight and general characteristics as possible on each occasion. Alternate animals were placed in the head-up and head-down position, as described.

The femoral artery was cannulated without the use of general anesthesia and a certain amount of blood was removed at hourly intervals. On each of the first three bleedings, an equivalent to 1 per cent of the body weight of the animal was removed; following this,  $\frac{1}{2}$  of 1 per cent of the body weight was withdrawn each hour, until the animal died. (This fractional method of bleeding was found to be more satisfactory for our purpose than any of several other methods tried.) Blood pressure and, in some instances, hematocrit determinations were made immediately after each bleeding, and the general condition of the animals was frequently observed. The total amount of hemorrhage before death was measured, and survival times were carefully noted. There was no replacement therapy. The temperature of the room in which the experiment was conducted was usually constant at 25° C., but varied on occasion between limits of 23 and 27° C.

## RESULTS

Fig. 1 shows the average amount of hemorrhage before death and the average survival times for each of the two groups of sixteen dogs used. On first examination, the figures might be interpreted to indicate a greater difference in the survival time of the two groups than in the amount of hemorrhage. This, however, is not the case, but is due to the smaller amount of blood withdrawn each hour in the latter part of the

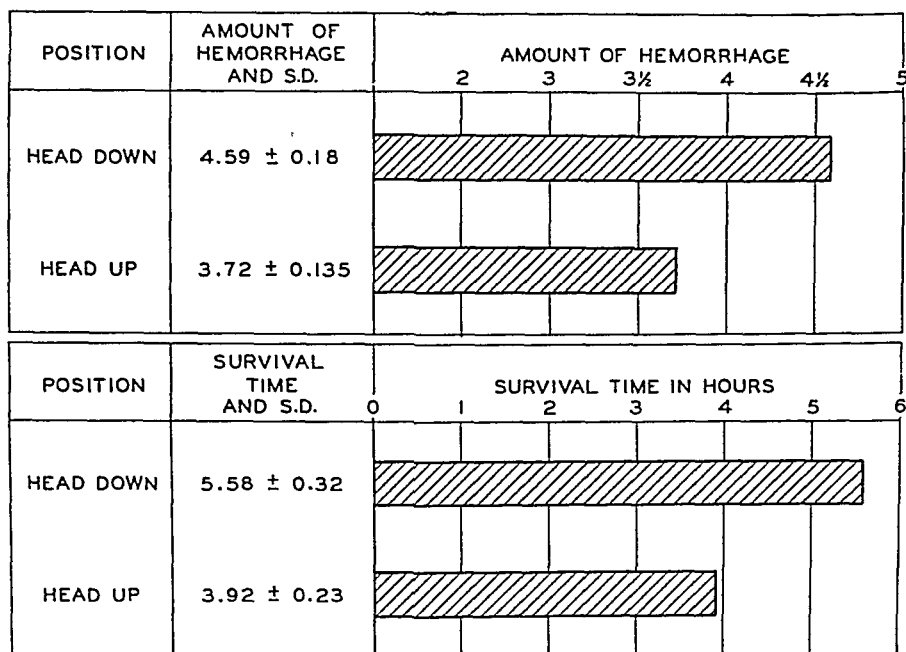


Fig. 1.—Mean amount of hemorrhage producing death, and survival times, for each of the two groups of dogs used in the experiment. Each figure represents the average amount of hemorrhage before death, or the average survival time for the sixteen animals in that particular group, with S.D. the standard deviation of the mean as calculated from statistical formulas. Amount of hemorrhage is expressed as percentage of body weight; survival time is given in hours.

experiment, as shown in the illustration. Average systolic blood pressure determinations for the two groups during the course of the experiment are given in Fig. 2, while Fig. 3 shows the average hematocrit figures for sixteen of the animals, eight from each group. It must further be noted that in general the animals with the head up seemed to remain alert and active until near the end, with death supervening suddenly, whereas those with the head down were quieter, became gradually less alert, and frequently were comatose for some little time before death.

## DISCUSSION

The difference between the mean amount of hemorrhage resulting in death for the animals with the head up and for those with the head down amounts to 19 per cent of the larger value. That this is of real

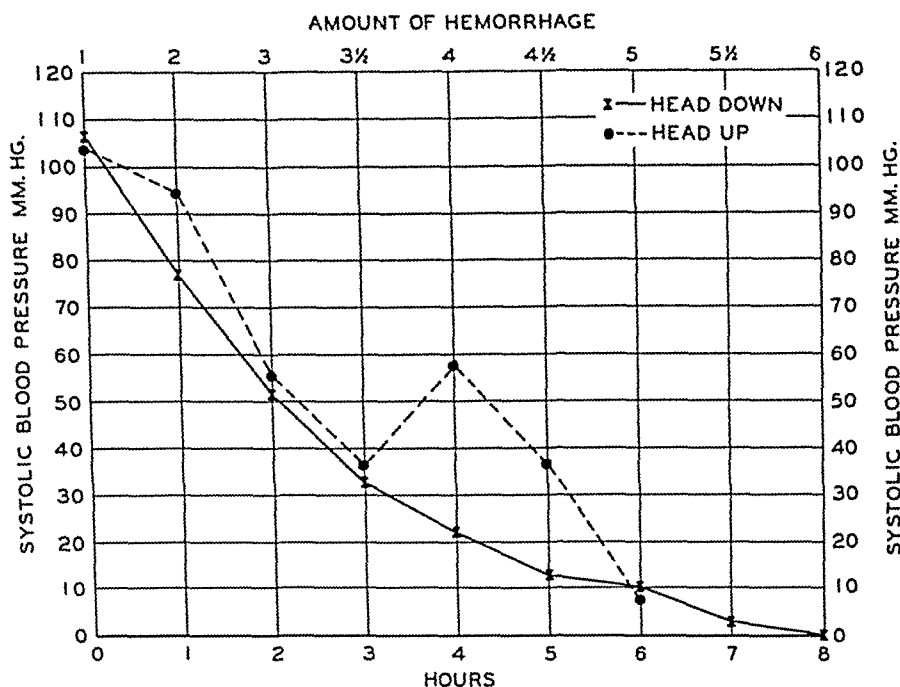


Fig. 2.—Average hourly systolic blood pressure readings for each of the two groups of sixteen animals.

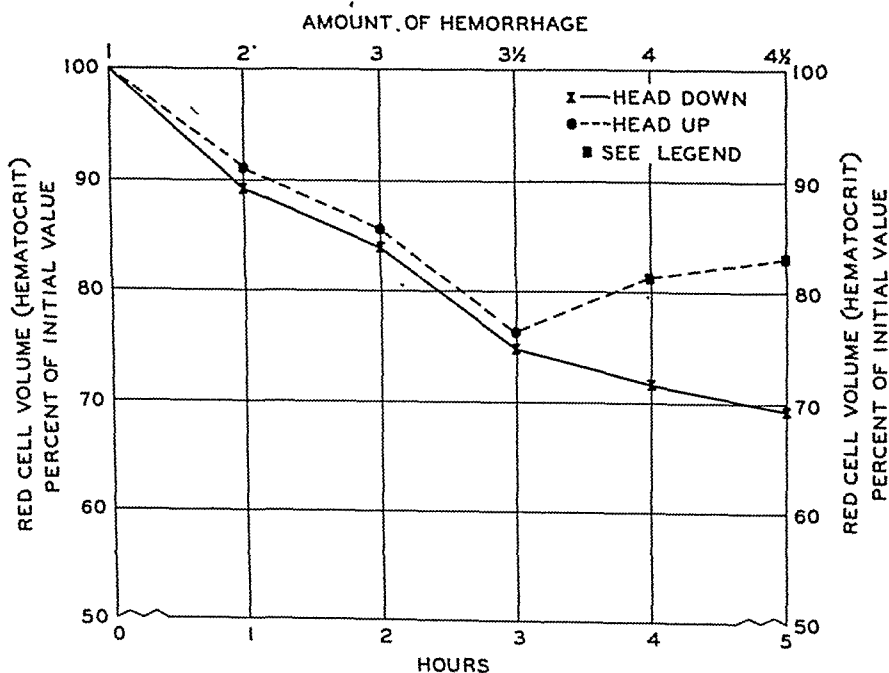


Fig. 3.—Average hourly hematocrit readings for each of two groups of eight dogs. The average initial values are represented as 100 per cent, and the following readings are given as percentages of the initial value. The last two values on the broken curve marked "■" are averages for four and three animals in the head-up group remaining alive at these respective times, and are not true representatives of the average of the whole group.

statistical significance is indicated by the standard deviations, as given in Fig. 1. Thus, it seems quite clear that dogs placed so that the head is elevated 30 degrees will survive some 20 per cent less fractional hemorrhage than will those placed with the head down 30 degrees. All environmental factors such as temperature are controlled by the performance of the experiment on the two groups under identical conditions. Therefore, it may be stated with some certainty that, within the limits of the experiment performed, lowering the head of the animal is beneficial in the treatment of shock produced by repeated hemorrhage at hourly intervals. It is true that the supine position is unnatural for a quadruped such as the dog, so that great caution must be exercised in attempting any clinical implications. It is known, however, that the blood pressure regulating mechanism for posture in dogs is similar to that in man, with adequate compensation occurring for postural changes of relatively short duration. Since the experiment herein reported was of an acute nature, lasting not longer than eight hours, it seems reasonable that the cardiovascular system of the dog may behave in a similar fashion to that of the human being under like circumstances.

No new light is afforded to explain the beneficial effect of the shock or head-down position by this experiment, but our results are consistent with the commonly held view that blood flow through the vital centers is maintained more adequately by lowering the head. The smooth blood pressure decline and gradual collapse of the animals with the head down, compared to the irregular blood pressure changes and more sudden death of those with the head up, suggests less uniform action of the integrated compensatory mechanisms involved, in the latter group.

The hematocrit determinations are probably not of much significance. The greater and more uniform decline of blood pressure in the head-down group would tend, by lowering capillary pressure, to promote the passage of fluid from the tissues into the vascular system, thus helping to produce the steadier decline in the hematocrit value already noticed, compared to the higher blood pressure and less hemodilution in the other group.

#### CONCLUSION

In the dog, shock produced by repeated small hemorrhages is beneficially influenced by the head down, Trendelenburg, or shock position. These findings may have some clinical significance; if they do, confirmation of the standard procedure of raising the foot of the bed in the treatment of shock is presented.

## SPOOL COTTON AS SUTURE MATERIAL

LIEUTENANT COLONEL JOE R. FLOYD, AND  
CAPTAIN MARK J. BROCKBANK, MEDICAL CORPS, U. S. ARMY

**S**POOL cotton was the only suture material used in 1,659 general surgical procedures. Our results are reported to lend emphasis to the observations of other workers and to stress certain advantages not generally appreciated which we believe accrue with the use of cotton. Our observation of these cases has caused us to view with enthusiasm the use of cotton sutures in most general surgery. The definite clinical advantages of wounds healing with minimal cellular reaction have been reported without stressing the surgical advantages which ensue with the use of cotton. We believe that these advantages become apparent with consideration of this fairly extensive series of cases.

Ordinarily, nonabsorbable sutures have been considered by many surgeons to be the only ones possessing "foreign body danger." Fear of this impels many to avoid the use of nonabsorbable sutures. Strain<sup>1</sup> emphasized the important fact that, absorbable or not, any suture is a foreign body. However, it is essential to realize that foreign bodies vary in the degree of local tissue reaction and that the absorption of absorbable suture induces much more tissue reaction than does the mere presence of nonabsorbable suture. We believe that the decreased tissue reaction of cotton far outweighs the "foreign body danger."

Meade and Long<sup>2</sup> have shown cotton to possess the desirable qualities of pliability, adequate tensile strength, a high coefficient of friction, and stability on exposure to heat and moisture. Meade and Ochsner's<sup>3</sup> investigation showed that cotton produced less cellular reaction than silk, linen, or catgut. Cotton is inexpensive, easily obtained, and readily transported. Special sterilization procedures are unnecessary providing care is taken to avoid fracture of the fibrils. This is readily accomplished by winding the cotton loosely on collapsible material such as rubber tubing.

The observations of these workers have been generally substantiated by others who have had considerable experience with cotton, and for this reason we had little hesitancy in adopting cotton for routine use as a suture material. Without exception, we have found that three sizes of spool cotton are adequate for general surgery. Size No. 60 is used for ligature of small vessels and occasionally for suturing wounds where the cosmetic result is important. Size No. 40 is used routinely for the closure of peritoneum, suture of bowel, stomach, muscle, subcutaneous tissue, and skin. Size No. 20 is used for the suture of

heavy fascia and the ligature of larger vessels and ducts. Stay sutures have never been considered necessary with cotton. Ordinarily, the peritoneum and skin are closed with a continuous stitch and all other sutures are interrupted. Care is taken to tie square knots and sutures are cut short. Cotton is finer than catgut and is technically more difficult to use. We believe this increases the surgeon's dexterity and meticulousness.

In one case of a recurrent inguinal hernia which we reoperated upon after nine months, the cotton sutures used in the first operation were difficult to find. There was but little fibrosis along the suture line in the external oblique fascia. The microscopic report showed mild fibrosis with minimal foreign body reaction about the suture. In all our experience we have seen no case of sensitivity or any unusual tissue reaction to cotton.

In this series of cases cotton was buried in every case and was the only suture material used. The postoperative wound complications were divided into two groups, a stitch abscess and a more severe infection. Of the 1,659 cases, 281 wounds were contaminated and 1,378 were clean. Of those contaminated, 11.4 per cent developed stitch abscesses and 3.6 per cent developed severe infections. Of the clean wounds, 2.1 per cent developed stitch abscesses and .5 per cent developed severe infections. Reference can be made to Table I to see the distribution of these complications.

At this point, it should be emphasized that only about two-thirds of all contaminated wounds at the hospital were closed primarily. Ordinarily, any wound with contamination over six hours old, regardless of how clean it might look, was left open, and in all which were closed primarily, a meticulous débridement was done. Sulfanilamide crystals were used locally in all contaminated wounds and, in addition, many patients received the drug orally.

All members of the surgical staff have been impressed by the fact that these wounds, clean or contaminated, showed much less induration, edema, and tenderness than we encountered in our work in civilian life, where almost without exception, catgut was the suture employed. The scars are soft and pliable and there is no distressing deep tissue induration which constantly reminds the patient of his incision. This fact is important from a military viewpoint, because we are convinced that the soldier pays less attention to his scar; and accordingly, the number of patients developing hypochondriacal ideas in reference to scars has been small. We have had three patients who have returned to the hospital complaining of pain in the incisional site to such an extent that they were unable to perform their duties. All three patients had other complaints which were not substantiated by the presenting pathology, and those patients were ultimately disposed of by the neuro-psychiatric service.

TABLE I  
DISTRIBUTION OF COMPLICATIONS

TYPE OF CASE	NO.	MINOR INFECTION	SEVERE INFECTION
Amputations			
Clean	3		
Contaminated	21	3	1
Appendicitis			
Acute	297	6	
Chronic	48	2	
Normal	19		1
Ruptured	27	2	4
Arthrotomies			
Clean	17		
Contaminated	3		1
Bone tumors	25		
Cholecystectomies	5		
Cysts and subcutaneous tumors	320	9	2
Foreign bodies			
Clean	5		
Contaminated	9	2	
Hernias			
Inguinal	282	4	2
Incisional	14		
Of muscle	17		
Epigastric	16	1	
Femoral	12		
Hydrocele	35		
Intestinal obstruction			
Acute	5		
Mastectomies	16	1	1
Perforated peptic ulcer	4		
Tenorrhaphies			
Contaminated	41	3	2
Thyroidectomies	4		
Varicose veins	214	6	1
Varicocele	24		
Wounds			
All contaminated	176	22	2
Total	1,659	61 (3.7% of total)	17 (1% of total)

As a routine part of the repair of inguinal hernias, the external and internal rings can be closed more snugly than was possible with catgut. This seems to be explained by the fact that the swelling produced by cotton is less and thus the rings can be more tightly closed without compressing the cord. Routine support of the testicle and cord is not necessary to prevent edema and discomfort.

Of our total of 341 hernias of all kinds, we have had four recurrences that we have been able to find. Two of these were femoral, which were operated upon through the subinguinal approach, and at the second operation an inguinal approach was made and neither recurred. Two inguinal hernias recurred and one was reoperated upon with a successful result; the other patient was separated from the service. To our knowledge, none of our laparotomy patients has developed an incisional hernia. We operated upon fourteen incisional hernias and fifteen recurrent inguinal hernias with no recurrences. One recurrent hernia had been operated upon three times, the fascia



lata being used twice. There was no recurrence after the fourth repair, and the patient was returned to full combat duty.

One patient with a bilateral hernia developed an acute bronchitis on the third postoperative day, and a bilateral pneumonitis on the seventh postoperative day. He coughed severely for seven days, but by the twenty-first postoperative day had made an uneventful recovery and four months later there was no recurrence of the hernia.

One patient with bilateral inguinal hernia developed a septic temperature on the fourth postoperative day with a fluctuant mass in the left incision. The skin sutures were removed and about 30 c.c. of thick creamy pus were evacuated and the wound was drained. The cotton sutures in the external oblique fascia remained in place and the wound healed without sinus formation and with no recurrence of the hernia. We have not observed in cotton the tendency toward sinus formation that exists in silk and chromic catgut.

One patient with a bilateral hernia developed a massive unilateral atelectasis with a severe cough. Bronchoscropy was used and 250 c.c. of mucus were removed by suction. A mild bronchopneumonia followed with complete recovery in three weeks. There was no complication of the wound and no recurrence of the hernia ninety days postoperatively.

It should be emphasized that all of the patients in this series were young men in excellent physical condition and were physically superior to the average civilian patient.

#### CONCLUSION

1. Spool cotton is an excellent suture material for all types of general surgery, including clean and contaminated wounds.
2. It is technically more difficult to handle than catgut and is thus conducive to meticulous surgery.
3. It possesses minimal "foreign body danger."
4. Induration, serum accumulation, and postoperative wound infections are minimal with cotton.

#### REFERENCES

1. Strain, Richard E.: Use of Cotton Thread As Suture Material, *Antiseptic* 38: 313-317, 1941.
2. Meade, William H., and Long, Carroll H.: Use of Cotton As Suture Material With Particular Reference to Its Clinical Application, *J. A. M. A.* 117: 2140-2143, 1941.
3. Meade, William H., and Ochsner, Alton: Spool Cotton As Suture Material, *J. A. M. A.* 113: 2230-2231, 1939.

## COTTON SURGICAL SUTURE MATERIAL

THEODORE L. HYDE, M.D., WICHITA FALLS, TEXAS

MANY surgeons are now using cotton thread as their routine suture material instead of surgical gut.<sup>1</sup> Other types of nonabsorbable suture material are becoming popular also, but evidence of the superiority of cotton has been rapidly accumulating in the past few years.<sup>2</sup> We expect that a full appreciation of the virtues of cotton will result in its wide adoption, with absorbable and other suture materials being used only where their particular qualities are specifically indicated.

We must avoid the mistake of learning again, now at our patients' expense, facts which were proved years ago. Nonabsorbable suture material was given a trial and rejected by the rank and file of surgeons fifty years ago when catgut first became available. The plebeian cotton thread was not given a serious trial then; it is very possible that if it had been, the course of surgical history would have been different.<sup>3</sup> The aristocrats of threads, silk and linen, were tried instead, but too often wounds repaired with them would become infected and drain for months until the sutures were extruded or removed. This seemed natural because after all the suture was a very foreign body. These draining sinuses were very embarrassing to the surgeon. Halsted, however, demonstrated that with careful technique fine silk sutures could be used which did not necessarily extrude with infection.<sup>4</sup> Few surgeons attained such perfection and even an occasional draining sinus was sufficiently discouraging to any surgeon in private practice. Catgut then was welcomed as a means of avoiding such embarrassment.<sup>5</sup> A superficial consideration accepted it as a more natural suture material. Of course, the surgical wounds became infected even more often and then the catgut might be extruded. The wounds were often painfully indurated, and occasionally disrupted entirely. These complications usually occurred promptly, however, and were not so obviously the fault of either the surgeon or the catgut.

The fact is that surgical gut can only be described as a very irritating substance to place in a surgical wound, the new fine sizes and recent improvements of manufacture notwithstanding.<sup>6</sup> It is irritating because of the large bulk necessary to hold the wound together and because of its chemical and biological constitution. In some patients the inflammatory reaction is so violent as to suggest an allergic reaction. Its only virtue is its transiency and the very process of absorption of it is deleterious to wound healing. Surgeons who have kept accurate records have reported infections in from 4 to 11 per cent of clean wounds when surgical gut is used.<sup>7-9</sup> Such wound infections are less than one-third

as frequent when cotton suture material is used.<sup>10</sup> Not only do fewer clean wounds become infected but many grossly contaminated wounds will gratifyingly and surprisingly heal cleanly.<sup>11</sup> Every operative wound is more or less contaminated, of course. The germs fall into it from the air, or in droplets from the respiratory passages. There may be breaks in the aseptic technique or they may enter the wound during transient bacteremias, which are more frequent than is usually appreciated. If the resistance of the wound has been impaired by trauma or by the presence of irritants such as surgical gut, infection commonly follows.

Other suture materials have been proposed. Isografts of fascia lata or cutis are possibly the least irritating of all but have obvious limitations. Various metal wires are well tolerated by the tissues chemically but are awkward to handle, radiopaque, more apt to cut through, and mechanically irritating by their stiffness. Silver wire was tried and abandoned too, years ago. Linen thread is the most irritating of the ordinary threads. Nylon is a generic name for synthetic chain-forming polymeric amides of a proteinlike chemical structure. There are literally hundreds of such substances possible. The thread we have tested has been supplied for surgical use and also some was purchased in a variety store. It has been well tolerated by the tissues but is very elastic and the knots are not dependable. Dermatitis from nylon hose is common enough to arouse suspicion of its irritating qualities.

Silk has been the most widely used and intensively studied of the various nonabsorbable suture materials.<sup>12, 13</sup> It is only mildly irritating chemically. Being essentially a straight fiber when it is spun or woven into thread, microscopic open dead spaces occur which harbor infection and are the mechanism causing the persisting draining sinuses. The minute stiff straight ends stick out from the main strand. As commercially supplied to the surgeon it is usually heavily impregnated with a paraffin wax. In spite of its disadvantages it has been earnestly advocated by very successful surgeons and Cutler has said that the occasional draining sinus is a small price to pay for the firmer healthier healing of the wounds.<sup>14</sup>

Cotton possesses all the virtues of silk without its disadvantages. It can be used in infected wounds without fear of its being extruded through chronically draining sinuses, provided it is properly placed. Its naturally curly fibers twist to form a compact thread.<sup>15</sup> Possibly because it is a vegetable carbohydrate rather than an animal protein it is not as irritating chemically. Placing short lengths of suture materials in the anterior chamber of the rabbit's eye has visibly demonstrated the minimal reaction of cotton.<sup>16</sup> Waxing is not necessary nor desirable. Size for size, dry, it is slightly weaker than silk but when wet it gains strength whereas silk loses strength. When in place in the tissues the cotton is as strong as silk. It retains its strength much better and does not swell. Regardless of the theoretical explanations or reasons, the

observed and demonstrated facts are that wounds repaired with cotton suture heal with maximal strength, speed, and comfort, and with minimal inflammation, infections, disruptions, and other complications.<sup>17</sup>

Cotton thread has been used extensively in commerce for many years and the best possible thread should already exist. However, the objective of the sewing trade has been a strong thread to be sure, but also a slippery thread which would slide easily through the cloth and the eye of a sewing needle. Moreover, if greater strength were necessary a slight increase in bulk was not so objectionable. The slipperiness has been obtained by singeing the loose ends off the thread in a gas flame and then adding wax or starch. An alizarin blue dye is commonly used to increase the whiteness and some soap may be left in the thread after the bleaching process. Mercerizing also produces a slippery thread with a high luster. Mercerizing is done by soaking the thread briefly in a strong caustic soda solution. This shrinks the thread and increases its strength although only in proportion to the swelling and increase in cross sectional area. The thread is kept under tension so it does not swell and shrink too much. The chemical nature of the thread is not changed but a different crystalline structure is induced and the thread is more absorptive.

The surgeon's problem is to find the strongest possible thread for size when tested knotted and wet and without the addition of irritating substances like starch, wax, dyes, soaps, etc. When cotton thread breaks, only about one-fourth of the fibers break and the rest of the fibers pull out. The advantage of a long fiber and a tight twist can readily be appreciated. The longest fiber is found in sea-island cotton (*Gossypium barbadense*) which is grown best under the climatic conditions found on the islands off the coast of the Carolinas and Georgia. This long staple cotton almost ceased to be available several years ago due to the ravages of the boll weevil. It is staging a comeback but only a very small amount is available. Its fibers range up to two and three-eighths inches long. The fibers of irrigated desert (Egyptian) cotton from Arizona, of which most thread is made, are about one and one-fourth inches in length. The ideal surgical suture cotton thread will some day be made out of long fiber Sea Island cotton meticulously carded to remove the short fibers, thoroughly bleached and washed to remove all impurities and natural oils, especially spun with an as yet undetermined twist to produce a maximum strength when knotted and wet, without kinking, and without the addition of any dye, starch, wax, or other filler. Such a suture of pure cotton fiber will approach the chemical innocuousness of tantalum wire and still be soft and stronger than any thread now available. Since no such thread is now available, for most of our work we have purchased ordinary plain white housewife's spool cotton sewing thread (Clark's O.N.T.) at a variety store. We have not been particularly dissatisfied with it except for the natural

desire for the best possible. This is a six-cord thread of good strength and containing very little extraneous substance. Technically it is a quilting thread although of soft finish. Most so-called quilting cottons are of a *glacé* finish impregnated with starch or wax. Although the full physiologic effect of mercerizing and the addition of dyes, starch, etc., has not been fully determined experimentally, and they are evidently not too irritating, they are at best unnecessary complicating factors. We have found slightly stronger threads but they were all contaminated with fillers and we have not felt that the slight additional strength justified their use.

We take advantage of the cheapness of cotton thread to facilitate its use. Its cost per operation is less than 2 per cent of that of silk or surgical gut. Cheapness is the least of its virtues, however; the operating table is no place for economy but rather that the best is none too good. We prepare it in skeins of thirty strands. The thread is wound thirty times around a wooden board cut with steps six, seven and one-half, and nine inches long. We use Size 60 in twelve-inch lengths as being the most convenient length for the one-handed tie. Size 40 is prepared in fifteen-inch lengths as a slightly longer strand allows the clamps on the ends of each stitch to hang further away from the incision. Larger sizes are prepared in eighteen-inch lengths. The various lengths serve to distinguish the various sizes although one soon becomes familiar with them. At one end of the board the bundle of thread is rubbed with paraffin and held momentarily against a hot sterilizer or autoclave. This melts the paraffin, which soaks into the thread. The bundle is then cut with a razor blade through the center of the paraffined area. This provides paraffin-stiffened ends to each strand which facilitates threading the needles. In use it works out that the paraffined ends are never left in the wound although it probably would not matter much if an occasional one was. The skein of thread is tied with a single strand at the middle and near each end so that the threads can be pulled out from the ends without snarling. The skein is coiled loosely on itself and tucked into a pocket of a prepared muslin envelope for sterilizing. These envelopes are made with four pockets for three sizes and a long strand of the skein. Additional supplies of various size threads are kept sterile in jars in the operating room. The thread is autoclaved although it can be boiled and used wet.<sup>19</sup> It is only sterilized once although it does not lose much strength on repeated autoclaving. It shrinks temporarily during sterilization and must not be wound on rigid spools.

Certain principles of surgical technique must be practiced when non-absorbable suture material is used. Mistakes such as improperly placed sutures which are only temporary as when held with surgical gut are eventually adjusted by the healing process. When errors of technique are perpetuated by permanent suture material they may have to be rectified subsequently by surgical removal of the strand. Gentleness in the

handling of tissue and accurate dissection are important regardless of the suture material used. One reward of carefulness is a reduced incidence of perforated gloves, one or more of which is perforated in at least 50 per cent of operations.<sup>15</sup> Vessels should be grasped with small pointed clamps. Ligatures should be placed upon just the vessel, avoiding the strangulation of large tags of tissue in the ties. A transfixing suture is often the best tie. Suture lines should be sewed with the smallest effective size of suture material and with the smallest effective bit of tissue in each stitch. Small needles with taper points are desirable, such as Mayo No. 6, Ferguson No. 10 or 12, and Kelly Intestinal No. 4. Tissues are to be opposed without dead spaces but also without squeezing else the sutures will cut through. Nowhere should a portion of the suture strand bridge across as a chord subtends an arc creating a dead space in which serum can collect. Continuous suture is less desirable than interrupted stitches if the latter are placed with uniform tension. This can be accomplished only by placing all the stitches in any one row before tying any of them. The wound is then held together by the assistant by traction of the untied strands so that beginning at one end of the incision each stitch can be tied in succession without tension. Wounds must be dry on closure and when drains are necessary they should exit through a separate stab wound and not through the suture line.

We have used cotton thread mostly in No. 40 for sutures and No. 60 for ligatures. No. 80 has been used for tendon suture and No. 100 for nerve suture. If tissues are sutured with more tension than No. 40 will hold, the stitch will probably cut through anyway. The exception to this is the upper abdomen where the stress of postoperative vomiting may require a stronger thread such as No. 20, or the wound may be reinforced with snugly tied stay sutures of No. 10. Beginners first adopting cotton should use larger sizes unless they have already had considerable experience with fine silk. Doubled strands should never be used. Experimental wounds contaminated with staphylococcus extruded the stitches only when the cotton thread was used double. The figure-of-eight stitch is undesirable because of the doubling at the crossing of the strands; their pulley action is unnecessary because wounds are held closed during the tying. Mattress stitches are frequently used, however. The tendency is to demand a larger thread for easier tying without regard for the requirements of the wound. The fine sizes are usually as strong as the tissues. Thirty or more needles are used and already threaded before the operation is begun. Each strand is used for but a single stitch or tie. The one-handed knot is almost essential since it gives substance to the delicate strands by keeping them under tension. Knots hold very well especially when wet, but are not infallible. We commonly use triple-throw knots and are careful to tie them square. This is very quickly done and almost automatic with the one-handed knot. With the fine sizes the knots are minutely small anyway. The ends are cut on

the knot less than 1 mm. long. The residual ends sometimes stick to the gloves and are troublesome to get rid of. They are more easily discarded if they are of some length. When the cotton thread is used dry and the knot pulled too tight the strand usually breaks in the dry part some little distance from the wet bloody knot. This leaves a short wet end near the knot of sufficient length to finish the knot with the use of artery forceps. We commonly use a continuous stitch for the skin as interrupted skin stitches seem unnecessarily meticulous. There is just enough "hang" to the cotton strand through the skin that the traction of an assistant on the skin stitch is unnecessary. Cotton thread pulls out very easily, and is quite painlessly removed from the skin and when used for deep stay sutures. It is superlative as a subcutaneous stitch for meticulous closures on the face because the strands easily pull out long distances if left in eight or ten days.

It is not to be denied that surgical gut and other suture materials are of value. Especially is this true of fascia lata in the repair of hernias.<sup>20, 21</sup> Wire will occasionally be desirable for its tensile strength as in bone work. Silkworm gut is still acceptable for stay sutures which traverse the entire abdominal wall. To change from surgical gut to cotton usually adds about 30 per cent to the operating time although this differential can be reduced by teamwork and skill.<sup>22</sup> Any prolongation of the operating time may not be justified in certain emergency operations, such as splenectomy for ruptured spleen, but hurry is the least valid excuse for poor surgical technique.<sup>23</sup> Anywhere that a continuous suture is very desirable, such as the gall bladder bed after cholecystectomy or the vaginal stump after hysterectomy, surgical gut should probably be used for suturing although we have used continuous cotton thread successfully for the serosal stitch of enteroanastomosis and (experimentally) in abdominal closures. Instances where very large bites of tissue are necessary, such as perineorrhaphy, may require surgical gut.<sup>24</sup> The intestinal mucosa tolerates poorly a continuous non-absorbable suture, and hemorrhoidectomies are preferably sutured with surgical gut. The urinary tract mucosa should not be sutured with permanent suture material. There is no inherent antagonism between surgical gut and cotton; one merely sacrifices the advantages of cotton with the use of the gut. There is probably no instance where silk is preferable to cotton.

The essential question is: can one use cotton or any nonabsorbable suture material in surgical wounds without risking the embarrassment of draining sinuses and having to remove each stitch later? The word embarrassment is used advisedly because usually the wounds heal firmly without hernia even with the sinuses.<sup>25</sup> It has been just this embarrassment which has precluded the universal acceptance of silk. Evidence is accumulating that when cotton is properly used it can indeed be used without fear of such embarrassing sinus formation. This does not mean

that in the profuse drainage of a severely infected wound there may not appear an occasional sloughed out cotton suture or ligature, but when the acute infection subsides no cotton suture in the depths of the wound will constitute a foreign body to preclude healing.<sup>26</sup> We have used cotton in infected wounds such as pilonidal cysts and in contaminated wounds as after appendectomy which occasionally became infected later, and have yet to remove an offending cotton stitch.<sup>27</sup> On the other hand we have removed many silk stitches and catgut strands. We have observed that healing infected wounds invariably granulate in, and cover without delay, buried cotton ligatures. We have been impressed with the rarity of infection in wounds repaired with cotton in patients whose appendix had ruptured or was gangrenous. This improvement may have been in part due to the benefits of sulfanilamide. We have admired the minimal inflammatory reaction in wounds repaired with cotton. Possibly the most convincing evidence of all is that we have observed reluctant surgeons habituated to surgical gut become enthusiastic over the superiority of cotton by observation of the results obtained.

Comfort is difficult to evaluate but one woman who had a low midline wound repaired with surgical gut, and seventeen days later a long right rectus incision repaired with cotton, voluntarily testified to the markedly less discomfort from the latter wound. This patient also had a single cotton stitch work up to the surface of the wound in the seventh week. No discomfort was associated with the event; in fact, she did not think enough of it to call or show it to her surgeon. A skin incision in the thigh for fascia lata had three small serum pockets appear in the eighth and ninth week which were punctured and drained for a few days. These resembled the common sequelae to the use of surgical gut. No fragments of cotton thread could be identified in the drainage and the wounds closed promptly. These two episodes have been the only late complications (if they can be called such) we have observed in an experience of using cotton for more than a year.<sup>28</sup>

There is an old adage that "Never is never true." We cannot say that cotton suture material will never cause a persistent discharging sinus until its strands are extruded, but we do believe the possibility of such an embarrassment to be so remote that we use cotton now when we were unwilling to use silk formerly. The implications of this fact are not readily appreciated but it is plain that potentially infected wounds particularly should be afforded the advantages of cotton suture. Surgical gut is least reliable and most unsatisfactory in the presence of infection. It does not survive to hold the wound together and serves as a culture medium for the invading organisms. Silk has been used in the presence of infection only with misgivings that each stitch would later have to be retrieved. Cotton sutures can be used without this fear but with assurance that they will hold the wound together throughout the infection and not deter healing after the infection subsides. Any in-



the knot less than 1 mm. long. The residual ends sometimes stick to the gloves and are troublesome to get rid of. They are more easily discarded if they are of some length. When the cotton thread is used dry and the knot pulled too tight the strand usually breaks in the dry part some little distance from the wet bloody knot. This leaves a short wet end near the knot of sufficient length to finish the knot with the use of artery forceps. We commonly use a continuous stitch for the skin as interrupted skin stitches seem unnecessarily meticulous. There is just enough "hang" to the cotton strand through the skin that the traction of an assistant on the skin stitch is unnecessary. Cotton thread pulls out very easily, and is quite painlessly removed from the skin and when used for deep stay sutures. It is superlative as a subcutaneous stitch for meticulous closures on the face because the strands easily pull out long distances if left in eight or ten days.

It is not to be denied that surgical gut and other suture materials are of value. Especially is this true of fascia lata in the repair of hernias.<sup>20, 21</sup> Wire will occasionally be desirable for its tensile strength as in bone work. Silkworm gut is still acceptable for stay sutures which traverse the entire abdominal wall. To change from surgical gut to cotton usually adds about 30 per cent to the operating time although this differential can be reduced by teamwork and skill.<sup>22</sup> Any prolongation of the operating time may not be justified in certain emergency operations, such as splenectomy for ruptured spleen, but hurry is the least valid excuse for poor surgical technique.<sup>23</sup> Anywhere that a continuous suture is very desirable, such as the gall bladder bed after cholecystectomy or the vaginal stump after hysterectomy, surgical gut should probably be used for suturing although we have used continuous cotton thread successfully for the serosal stitch of enteroanastomosis and (experimentally) in abdominal closures. Instances where very large bites of tissue are necessary, such as perineorrhaphy, may require surgical gut.<sup>24</sup> The intestinal mucosa tolerates poorly a continuous non-absorbable suture, and hemorrhoidectomies are preferably sutured with surgical gut. The urinary tract mucosa should not be sutured with permanent suture material. There is no inherent antagonism between surgical gut and cotton; one merely sacrifices the advantages of cotton with the use of the gut. There is probably no instance where silk is preferable to cotton.

The essential question is: can one use cotton or any nonabsorbable suture material in surgical wounds without risking the embarrassment of draining sinuses and having to remove each stitch later? The word embarrassment is used advisedly because usually the wounds heal firmly without hernia even with the sinuses.<sup>25</sup> It has been just this embarrassment which has precluded the universal acceptance of silk. Evidence is accumulating that when cotton is properly used it can indeed be used without fear of such embarrassing sinus formation. This does not mean

7. Cannady, John E.: Discussion of Barker, W. Halsey, *Surgical Aspects of Chemotherapy*, West Virginia M. J. 39: 8-14, 1943.
8. Meade, William H., and Ochsner, Alton: The Relative Value of Catgut, Silk, Linen, and Cotton as Suture Materials, *SURGERY* 7: 485, 1940.
9. Elkin, Daniel C.: Wound infection: A Comparison of Silk and Catgut Sutures, *Ann. Surg.* 112: 280-283, 1940.
10. Guthrie, Donald, Brown, M. J., and Woodhouse, K. W.: The Advantages of Silk in General Surgery, *New York State J. Med.* 39: 2011, 1939.
11. Sparkman, Robert S., and Williams, William H.: The Employment of Cotton Suture Material in the Field, *SURGERY* 11: 698, 1942.
12. Shambaugh, Philip: The Silk Technique. Experimental Observations, *SURGERY* 7: 9, 1940.
13. Whipple, A. O.: Use of Silk in the Repair of Clean Wounds, *Ann. Surg.* 98: 662, 1933.
14. Cutler, Elliott C., and Dunphy, John E.: The Use of Silk in Infected Wounds, *New England J. Med.* 224: 101, 1941.
15. Thorek, Phil, Gradman, Ralph, and Glaess, Alfred: Additional Experiences With Spool Cotton as a Suture Material, *Am. J. Surg.* 59: 68-71, 1943.
16. Farris, John M.: Tissue Reaction to Suture Material as Observed in the Rabbit's Eye, *Univ. Hosp. Bull., Ann Arbor* 7: 61-62, 1941.
17. Localio, S., Arthur, and Hinton, J. William: The Choice and Use of Cotton for Suture Material, *Surg., Gynec. & Obst.* 72: 615, 1941.
18. Weed, Lyle A., and Groves, Jessie L.: Surgical Gloves and Wound Infections, *Surg., Gynec. & Obst.* 75: 661-664, 1942.
19. Pennett, Charles A.: Plea for the War-Time Use of Cotton Ligatures, *Lancet* 1: 755, 1942.
20. Gray, W.: The Operative Treatment of Inguinal Hernia, *Brit. M. J.* 1: 568, 1940.
21. Guthrie, Robert F. Olson, John D., and Masson, James C.: Results of Use of Fascial and Nonfascial Sutures in Hernial Repair, *S. Clin. North America* 23: 1177-1189, 1943.
22. Taylor, K. P. A.: Single Unit, Cotton Thread Surgical Technic, *South. Surgeon* 10: 125, 1941.
23. Lupton, Charles H.: Principles of Surgical Technique. With Particular Reference to the Use of Silk, *Am. J. Surg.* 45: 309, 1939.
24. Hudgins, A. P.: Perineal Repair With Cotton and Postoperative Sitz Baths, *West Virginia M. J.* 37: 309, 1941.
25. Marbury, William B.: Post-Operative Herniae, *Am. J. Surg.* 59: 60-67, 1940.
26. Thorek, Phil: Experiences With Spool Cotton as a Suture Material, *Am. J. Surg.* 55: 118, 1942.
27. Taubenschlag, Herman: The Advantages of Cotton Thread as Suture Material, *Prensa méd. argent.* 28: 1504, 1941.
28. Taubenschlag, Herman, and Reaux, Alberto Raul: One Year's Experience With Cotton as Suture Material, *Prensa méd. argent.* 29: 741, 1942.

# SURVIVAL OF RHESUS MONKEY FOUR YEARS AFTER EXCISION OF HEAD OF PANCREAS WITH OCCLUSION OF EXTERNAL PANCREATIC SECRETION

ALEXANDER BRUNSCHWIG, M.D., CHICAGO, ILL.

(From the Department of Surgery, The University of Chicago)

SINCE it has now been repeatedly demonstrated that resection of the entire duodenum and head of the pancreas with occlusion of external pancreatic secretion is feasible in man with immediate survival in good condition, the question is raised of the possibility of indefinite survival under these conditions.

Excision of the head of the pancreas with ligation of the neck was carried out in Rhesus monkeys and the observations reported elsewhere.\* The body and tail of the pancreas distal to the ligature were converted into an elongated cystic structure not more than 1 cm. in diameter and of approximate length of the original organ, as a result of dilatation of the main pancreatic duct. There was complete atrophy of acinar tissue, and numerous rather large islets persisted in the cyst wall.

One of the monkeys survived for four years. Its history follows.

Male *Macaca rhesus* of unknown age. In March, 1940, laparotomy was performed and the head of the pancreas excised. The neck, at the level of the superior mesenteric vessels, was closed by a silk ligature. It was possible to excise the head without injury to the common duct as it entered the duodenum. The main pancreatic duct was ligated and divided at the point of entrance into the duodenal wall. The blood supply of the duodenum remained intact. Fourteen months later a second laparotomy was performed to inspect the upper abdomen. The liver appeared normal. The body and tail of the pancreas had become an elongated cystic structure with transparent walls. The site of the head of the pancreas was cicatrized but there had not been sufficient contracture to approximate the stump of the neck to the duodenal wall. There was no evidence of pancreatic regeneration from the duodenal wall at the site of the ligated distal stump of the duct of Wirsung (which apparently had atrophied).

The animal's condition remained satisfactory. He ate normally of the stock diet which consisted of bread, greens, bananas, lung stew, and sometimes milk. There was no diarrhea. On several occasions the fasting blood sugar was within normal limits. Early in March, 1944, he appeared to be ill and depressed. March 21, 1944, he was found dead in his cage.

Necropsy revealed pulmonary congestion. The abdomen contained no free fluid. The liver was grossly normal. The gall bladder and bile passages were normal. The alimentary canal was normal; there were no ulcerations. The site of the head of the pancreas was occupied by strands of fibrous tissue (Fig. 1). The body and tail of the pancreas had the appearance of an elongated cyst with translucent walls 4.5 cm. in length and 1 cm. in greatest diameter. On its surfaces were small,

Received for publication, April 3, 1944.

\*Brunschwig, A.: The Surgery of Pancreatic Tumors, St. Louis, 1942, The C. V. Mosby Co., p. 63-74.

thin, irregular patches of dull yellowish tissue. The ligature at the neck of the pancreas was identified at the site of original placement. Inspection of the duodenal wall failed to reveal the site of the ligated terminal portion of the main pancreatic duct. There was no gross evidence of regenerated pancreatic tissue in the site previously occupied by the head of the pancreas. The neck of the pancreas was not approximated to duodenal or jejunal walls. There was no gross evidence of ducts from the occluded neck of the pancreas to bowel walls. The immediate cause of death was not apparent.



Fig 1.—Necropsy specimen of *Macaca rhesus* monkey four years after excision of head of pancreas and ligation of stump. *S.*, stomach, *Sp.*, spleen, *P.*, body and tail of pancreas converted into elongated cyst, *D.*, duodenum (opened) with metal probe in common bile duct protruding from ampulla, *A.*, *H.*, fibrous tissue in site previously occupied by head of pancreas, *M.*, superior mesenteric vessels. There is no evidence of pancreatic parenchyma, nor evidence of ducts between the occluded neck of pancreas and bowel walls (jejunum, duodenum). The stump of the main pancreatic duct ligated near the duodenal wall four years previously has atrophied completely.

Histologic studies revealed normal liver. Sections through the duodenal wall in the region of the ampulla showed no evidence of pancreatic ducts or acini. Multiple sections through the cicatrized tissue at the site previously occupied by the head of the pancreas revealed no pancreatic acinar tissue nor ducts. Sections at the proximal tip of the cyst replacing pancreas showed no acinar tissue or proliferating ducts. The wall of the cyst, which contained a clear gelatinous fluid, was composed of fibrous tissue and exhibited clumps of ducts appended to some of which was an occasional clump of cells resembling a pancreatic acinus in resting stage. The walls also contained scattered islets of Langerhans.

#### DISCUSSION

In the monkey described, permanent atrophy of acinar tissue of the body of the pancreas followed excision of the head and ligation of the neck of this organ. Islets survived and apparently functioned to permit

normal carbohydrate metabolism. Contrary to observations reported for the dog, that regeneration of pancreatic tissue occurs from small fragments of such parenchyma that may remain on the duodenum or that may result from proliferation of the stump of the main duct, no evidence was found in this monkey that regeneration of acinar tissue occurred from the ligated terminal stump of the duct of Wirsung or that such regeneration occurred from the body of the pancreas occluded for a prolonged period (four years). Furthermore, in this animal there was no evidence of duct proliferation from ligated stump of the body toward the adjacent duodenal or jejunal walls.

Survival for four years of one monkey was thus possible in the absence of pancreatic acinar tissue and with the absence of external pancreatic secretion. There was no evidence of significant physiologic disturbances during this period.

## HEMOSTATIC GLOBULIN AND PLASMA CLOT DRESSINGS IN THE LOCAL TREATMENT OF BURNS

LAURENCE MISCALL, M.D.,\* NEW YORK, N. Y.  
AND AUSTIN JOYNER, M.D., PEARL RIVER, N. Y.

CURRENT literature reveals a multiplicity of methods and theories in the local treatment of burns. The listing of at least thirty-seven different methods attests to some obvious confusion and inadequacy. The magnificent progress in systemic treatment made possible by basic discoveries in pathologic physiology and pharmacology have not been paced by similar improvement in local treatment. Recent return to favor of some of the older methods, such as petrolatum gauze and saline dressings, gives the impression that there is still much to be desired. Certainly no single treatment has been found satisfactory or applicable to all areas of the body even for burns of like degree.

Ideal local treatment should satisfy these criteria:

1. Trauma to the already damaged tissue must be minimal. This is particularly important for the remaining seeds of tissue since the damage can be repaired only by regeneration from this origin or by plastic replacement from others.
2. It should prevent plasma loss and other factors leading to shock.
3. It should be adaptable to the various requirements of function and structure of different parts of the body to insure good functional end results.
4. It should not predispose to nor trap infection.
5. Bacteriostatic activity and reduction of pain are essential.

It is believed that a plasma clot dressing has virtue because it may satisfy a maximal number of these principles. It is no more than an attempt to preserve the damaged tissue in a state conducive to rapid healthy recovery. It is no substitute for intelligent plastic surgery and certainly there is no desire to claim that results obtained are due to any dynamic properties of the method. Essentially the method consists of using a plasma clot to form a surgical dressing. The eschar covering the burned area is practically a physiologic dressing and should interfere minimally with the local physiology already disturbed by heat. The method is outlined here in order that its value may be quickly assessed in the hands of others.

Strips of sterile fine mesh gauze bandage (4 by 8 inches) are placed in a sterile basin. Preserved blood plasma from pools, banks, etc., is rapidly mixed with a solution having thrombic activity and then poured over the gauze in the basin. In a short time a plasma clot

\*Second Surgical Division, Bellevue Hospital.  
Received for publication, April 3, 1944.

gels on the gauze. The burned area has previously been débrided and cleaned with dilute soap and saline solution after opening all vesicles. The gel impregnated gauze is then accurately layered over the burned area after sprinkling very lightly with sulfadiazine powder. Extreme care must be used to sprinkle the powder lightly and not allow clumping. Over the plasma clot dressing is then placed a snug dressing of sterile gauze reinforced with elastic bandage to provide pressure. The absorption of serum by the heavy gauze permits the dressing to dry in from six to twelve hours.

Results at this early date in a few patients with severe burns of the face, hands, and body have been more than gratifying. Pain has been uniformly absent. The dressing became stiff and adherent over healthy areas and remained so until softened and removed by wetting with saline solution. This, with pressure, prevented surface and tissue plasma loss and may have favored rapid and healthy epithelization. Infection has been absent or easily controlled since the plasmolytic action of bacteria allows easy detection by softening of the dressing. Such areas were readily lifted and treated. Although the clinical material with which to study this method has been limited, it is felt that the results to date justify a larger and more extensive trial.

The dressing has been prepared by several different methods. A preliminary dressing of plain plasma-soaked gauze in which the plasma was precipitated by chemical agents such as tannic acid and silver nitrate has been used. This method was discarded because the dressing became extremely hard and difficult to remove. The anticoagulant activity of sodium citrate in the plasma might be corrected by addition of calcium chloride. Since there are numerous objections to the use of any such chemicals in burned areas, thrombic activity has been employed to clot the plasma. This thrombic activity is obtained from a commercially prepared "hemostatic globulin" derived from rabbit's plasma and having the activity of thrombin. It has been found that 10 c.c. of 10 per cent solution of the hemostatic globulin will clot 100 c.c. of plasma firmly in from three to ten minutes. Since plasma preparations vary considerably, the strength of the plasma clot is controlled by varying the amount of hemostatic globulin and the time of action. The standard liquid intravenous human plasma which has been used might be replaced since the ability to clot and sterility are the only necessary prerequisites. Plasma containing precipitate making it unsatisfactory for intravenous use before filtering or plasma containing pyrogens could be employed. Either bovine or equine plasma, though untried, should be satisfactory if sterile. Both have been used intravenously in human beings. It is possible that a thicker and firmer clot could be obtained with a frozen or dried product by reconstituting it with a limited amount of water. The possibility of a mixture of powdered plasma and globulin impregnated on gauze is most attractive. The observation that the blister fluid in

several cases could be easily clotted prompted the use of the hemostatic globulin alone in several cases. This was also varied by spreading a plasma-moistened gauze dressing over the burned area and then spraying the gauze with the hemostatic globulin. If these variations are as successful as the heavier plasma clot method, they will represent a very practical saving of material. At this time they appear to be more practical for burns of a light degree.

#### SUMMARY

A method of preparation of a plasma clot dressing has been described and variations discussed. The method involves the clotting of plasma over gauze by means of hemostatic globulin. Plasma clot dressings prepared in this manner, and hemostatic globulin alone, have been used in the local treatment of burns. Encouraging early results indicate the desirability of further trial of these procedures.



## TRANSLUMBAR AORTOGRAPHY—AN APPARATUS FOR INJECTING THE RADIOPAQUE MEDIA

A. KELLER DOSS, M.D., FORT WORTH, TEXAS

ONE of the fundamental requirements for the production of a satisfactory abdominal arteriogram is the adequate concentration of radiopaque media within the arteries at the instant the roentgenographic exposure is made.<sup>1, 2</sup> In order to accomplish this, 15 to 20 c.c. of the media must be injected into the aorta within four to six seconds. An apparatus capable of exerting three atmospheres (45 pounds) of pressure on the fluid to be injected has been found essential.

The apparatus\* (Figs. 1 and 2) herein described is of simple construction, compact, easily sterilized, and accessible to anyone who can secure the services of a metal lathe operator. It is built about a one-quart blowtorch which serves to generate and supply the required pressure as well as support the cartridge in which the media is contained.

A one-half inch, three-way, airtight stopcock is screwed into the opening from which the heat-generating mechanism of the torch has been removed. To the horizontal nipple of the cock is attached, by means of a small, one-half inch brass elbow, an air gauge capable of registering 50 pounds of pressure. A one-half inch elbow is connected to the remaining opening in the cock. The cartridge, which contains the radiopaque media, is joined to the male end of this elbow by means of a tapered screw male and female coupling. The connection, which may be easily and rapidly adjusted with the bare fingers, insures an airtight union and at the same time is sufficiently strong to support the cartridge. The Luer lock, one way stopcock attached to the lower end of the cartridge, allows union with a piece of stiff tubing which in turn joins by Luer lock the cartridge to the needle inserted in the aorta.

The chamber in which the radiopaque media is placed is constructed about a thick-walled "urea tube" converted into a cylinder by grinding away the bottom. The cylinder is then snugly fitted into a jacket made from a piece of one-inch brass pipe in which two windows are cut opposite each other in order to allow adequate visualization of the media. Projection of each end of the cylinder, about one-sixteenth inch beyond the brass jacket, is arranged to allow proper cushioning of it against rubber gaskets contained in two brass caps which are screwed on each end of the metal jacket. The upper cap serves to support the cartridge as well as connect it with the pressure chamber. The lower cap supports a one-way stopcock with Luer lock. After the cartridge is assembled the glass cylinder is calibrated at 5 c.c. intervals.

Received for publication, March 29, 1944.

\*Constructed by Terrell Supply Company, Fort Worth, Texas.

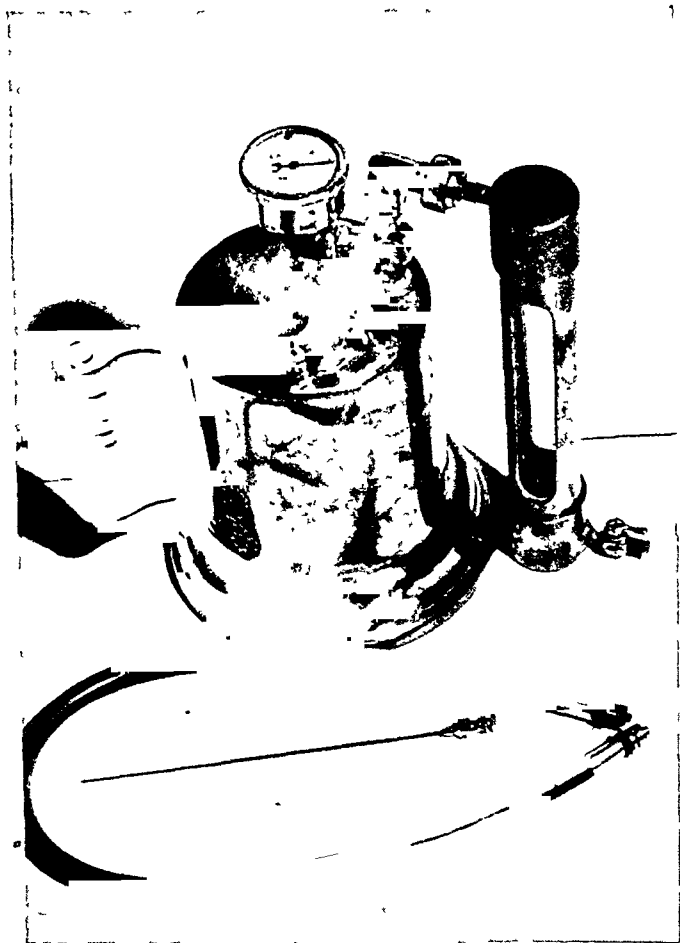


Fig. 1.—Photograph showing the pressure chamber and cartridge assembled.

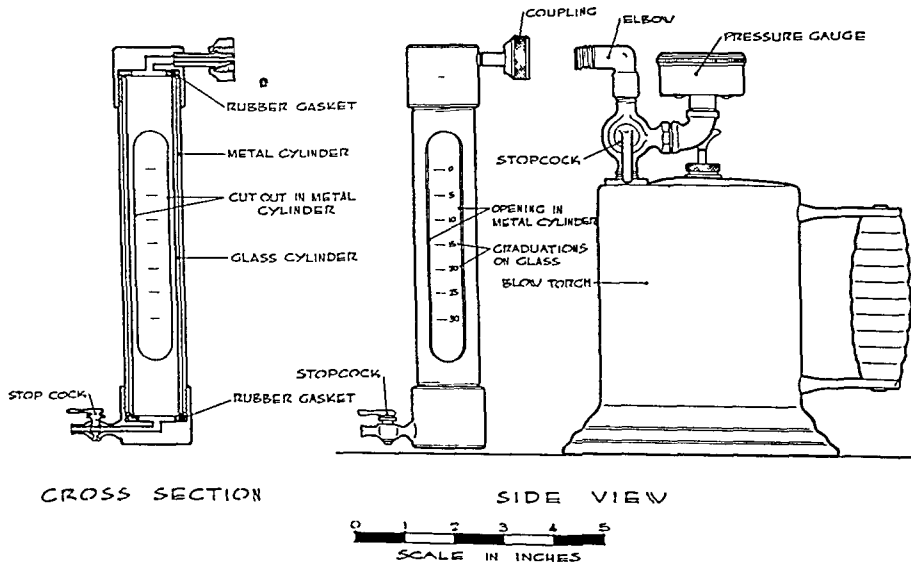


Fig. 2.—Sketch showing apparatus

The capacity of the chamber is such that it will accommodate slightly more than 60 c.c. of fluid, an amount sufficient to provide a safe margin beyond the 15 to 20 c.c. of fluid to be injected, therefore reducing to a minimum the danger of introducing air into the aorta. Filling of the sterile cartridge is accomplished by locking the tubing to the one-way cock and injecting the media to the required level in the cylinder in a retrograde fashion. Expulsion of all air from the apparatus results at the same time. The one-way cock is then closed. With the tubing attached the cartridge is readily connected to the pressure chamber through use of the screw coupling. The 45 pounds of pressure generated in the torch by the built-in pump is then applied to the fluid by adjusting the three-way stopcock. The speed of the flow as well as the amount of fluid to be injected into the aorta is controlled by the one-way cock at the lower end of the cartridge.

The needle used to puncture the aorta is of special construction. It is made from 18 gauge stainless steel tubing and is 7 inches in length.

#### REFERENCES

1. Doss, A. Keller, Thomas, H. C., and Bond, Tom B.: Renal Arteriography, Its Clinical Value, *Texas State J. Med.* 38: 277-280, 1942.
2. Doss, A. Keller: Renal Hypertension: The Value of Translumbar Arteriography in Its Diagnosis, *Texas State J. Med.* 39: 188-194, 1943.

---

#### Notice

References for the article on page 181 of the August, 1944, issue, "The Relationship of Hormones to Testicular Tumors" by Gray H. Twombly, M.D., New York, N. Y., will appear at the end of the reprints.

# Editorial

---

## The Story of the Kenny Method

JUST three and one-half years ago, in 1940, a distinct change in our treatment of infantile paralysis was introduced, one that has since caught the public's attention because of its human drama. This was, of course, the method of treating infantile paralysis victims which was evolved by Sister Kenny, the Australian nurse.

Many have misunderstood the nature of the Kenny treatment, and have thought it a cure for infantile paralysis. That is not true, and Sister Kenny makes *no* such claim. There is no cure for this crippling disease. The medical profession is still in the dark as to how to prevent it. It cannot control its spread. No one yet knows by what method this virus is carried from one victim to another. In a day when we are masters of malaria, smallpox, and diphtheria, infantile paralysis is still a riddle, a mystery, a crippling menace prowling our country at will.

What Sister Kenny *has* contributed, however, and it is a very real contribution, is a method for treating victims already stricken by infantile paralysis; a method that in the opinion of many American doctors reduces the crippling aftereffects of the disease.

There is a real interest in the history of the Kenny method in this country, and The National Foundation for Infantile Paralysis played an all-important part in evaluating this technique and in making it available to every infantile paralysis victim.

Sister Kenny went to the offices of the National Foundation one day in May, 1940, because she knew that the job of the National Foundation was to examine and study every new bit of knowledge that could possibly hasten the conquest of infantile paralysis. Present that day were Sister Kenny, the President of the National Foundation, and its Medical Director. Sister Kenny told how she had first developed her method. Thirty years before, as a young nurse in the Australian bush country, without medical assistance she had to care for a child stricken with infantile paralysis. Instead of immobilizing her patient's paralyzed limbs in casts or splints, she worked out a method of easing the pain and tightness in the muscles by frequent applications of heat—strips of woolen material were wrung out of steaming hot water. As the pain subsided she followed this with passive exercise until the patient himself could move his limbs. She felt that in many cases, this treatment had prevented many of the crippling aftereffects of the disease.

Sister Kenny was anxious that the National Foundation subject her method to scientific check, and so was the National Foundation. A few weeks later, when the University of Minnesota asked the National Foundation to support a program to study the Kenny method, it readily made a grant to that institution to enable Sister Kenny to demonstrate her method, and to give the doctors at Minneapolis a chance to see her work. For the next six or seven months, Sister Kenny treated infantile paralysis patients in Minneapolis.

In January of 1941, the National Foundation received a preliminary report from the doctors at the University. They were strongly impressed by what they had seen. To be sure, the number of cases studied had been few—too few to justify definite conclusions, but the physicians supervising this study felt that the patients treated had made far better recoveries than was usual in their experience. They recommended further study.

There was one fact, not widely known, that made these doctors cautious in their judgment. And that was the fact that over 50 per cent of all infantile paralysis patients seemingly recover by themselves, without any special form of treatment! "How do we know," these doctors asked, "That many of these patients Sister Kenny has treated might not have been among those that would have recovered spontaneously?" Obviously no one could answer that question, but medical science and the National Foundation had to take that factor into account.

The caution of these doctors making their first study of the Kenny method was justified on other grounds, too. They had seen many hopeful methods for treating infantile paralysis tried before—methods which failed to stand up under scientific test. Before they gave the Kenny method their full approval, they had to be sure.

That is why, in 1941, the National Foundation made a second grant to the University of Minnesota to make further studies of the Kenny method. Nearly 100 patients were treated the following year. In December of 1941, the medical men of the University made a second report. After consideration of this report, the Medical Advisory Committee of the National Foundation declared:

"It is the opinion of this committee that during the early stages of infantile paralysis the length of time during which pain and tenderness are present is greatly reduced, and contractures caused by muscle shortening during this period are prevented by the Kenny method. The general physical condition of the patient receiving this treatment seems to be better than that of patients treated by some of the other methods during a comparable period."

It was on the basis of this report that The National Foundation for Infantile Paralysis felt justified in opening the throttle and going full steam ahead to make this Kenny method of treating infantile paralysis available everywhere in the land. A plan was immediately set up to

instruct and train doctors, nurses, and physical therapy technicians. Sister Kenny herself was to help in the teaching at the University of Minnesota.

How well this has worked was clearly demonstrated during the epidemics of 1943 when 12,404 cases were reported. The doctors of the whole nation had learned something of the work; many were intimately acquainted with it. Physical therapy technicians and nurses had been trained to do the work. From the epidemic areas of the West, the Central States, and the East came a flood of requests from physicians for more technicians and more nurses to give this treatment.

Here was proof of the endorsement of the method by American medicine! Patients could be treated from coast to coast. Private physicians, clinics, hospitals, and departments of health called for more skilled workers. The supply was limited by the demands placed on this country by war; yet there were enough to do a good job.

Up to the present time, a total of 900 persons have received this training at the University of Minnesota alone, and have been graduated with the approval and certification of Sister Kenny.

All of this has been tremendously costly—a cost borne entirely by the National Foundation. To date, \$107,000 has been given by the National Foundation to the University of Minnesota alone, to further the evaluation and teaching of the Kenny method. Every sum this University has ever requested has been granted in full by the National Foundation.

But the task of teaching the number of technicians needed to serve the whole country was too great for any one school. So the National Foundation opened other centers. Institutions in California, Illinois, Indiana, Georgia, Pennsylvania, and New York took up the teaching of the Kenny method. In addition to the money given to the University of Minnesota, \$140,000 has been granted to the other schools. These grants were made to schools connected with or operated by medical teaching centers. Eight medical colleges and one hospital devoted solely to treating infantile paralysis and to training professional people took up the burden of making the special skills and knowledge available to all doctors, nurses, and physical therapy technicians. There was no quarrel here between American medicine and new methods of alleviating suffering and crippling from infantile paralysis!

The National Foundation has spent additional money on scholarships, wool for treatment, distribution of literature, exhibits, and demonstrations—a total of \$301,000.

In fact, and it is one worth remembering, in the past three years the National Foundation and its Chapters have spent a total of over one-half million dollars of your money for the study and teaching of the Kenny method. It is no exaggeration to state that in all the history

of medicine, few new theories have ever received such generous financial support from the people of any nation.

In addition to all of the foregoing, two five-year grants have been made recently by the National Foundation: one for \$175,000 to the University of Minnesota to study the physiologic problems concerning the mechanism of infantile paralysis and methods of treatment; the other for \$150,000 to the University of Pennsylvania to establish a center for research and instruction in physical medicine. Both of these grants permit further evaluation and teaching of the Kenny method.

It is the dimes and dollars of the American people that have made this possible—the dimes and dollars they have contributed each year to the March of Dimes. And those dimes have done good work. Last year, the third greatest epidemic in the recorded history of the disease in the United States struck our country. Had it not been for the hundreds of doctors, nurses and technicians trained with the public's money and ready to administer the Kenny method promptly, that epidemic might have resulted in a national disaster.

It is obvious, of course, that this newer type of treatment is far more costly, in money and personnel, than the older systems of handling victims of poliomyelitis. Heretofore, patients were usually immobilized in splints and plaster casts and could be cared for by a small staff of doctors, nurses, and technicians. The physical therapy given usually consisted of a few hours of treatment a week, and that frequently was administered only late in the disease.

With the Kenny method, all that is different. Our medical men, in their own language, describe the Kenny method this way: "It is the early use of physical therapy, designed to prevent unnecessary deformities and to bring about the maximum function of such nerves and muscles as may have been spared by the disease process."

That means that each patient must have far more individual attention. Each must have hot packs applied every hour or two for at least twelve hours of the day during the acute stages of the disease. At the same time, the passive exercise and re-education of the patient's muscles must be started. Just consider the personnel required to provide such care under epidemic conditions. Consider, too, the soaring cost of such treatment.

Progress is being made in the fight against infantile paralysis. The Kenny method definitely represents an important step forward in our treatment of this disease. But the fact that it is *not* a cure and it is not fully developed must be borne in mind.

There are some patients who cannot be helped at the present time by any known method of treatment, whether it be the Kenny method or any other. These are the victims whose nerve cells have been completely destroyed by the ravages of the disease. To them, motion in some muscles has been denied forever. It is for these cases, particularly, that the

research programs of the National Foundation, designed to find a way to prevent the disease, must go on.

Unfortunately, no one has yet been able to find a cure for infantile paralysis. Studies are constantly being pursued along this line by the National Foundation, but so far without result. There is no known drug or serum or vaccine to combat the virus that causes the disease. But, in the meantime, both the amount and kind of palliative treatment have been improved.

How such treatment methods can be best taught and made available to the people is a matter about which there is a difference of opinion. The establishment of a Kenny institute in Minneapolis as the only place where the Kenny method would be taught has been suggested. But, of course, it is impossible to train all the Kenny technicians we require at any one place, in Minneapolis or elsewhere. And it would be equally impossible for any one person to supervise the various centers of teaching now supported by The National Foundation for Infantile Paralysis.

The ultimate aim is to make whatever is sound in the Kenny method a part of the curriculum of every medical, nursing, and physical therapy school in the country—and that aim will be accomplished. No one institution can have a monopoly on the teaching of the Kenny method. While it is Sister Kenny's contribution to humanity, for humanity's sake it must be available to all.

This history of the Kenny method shows very clearly that the National Foundation stands ready to evaluate and test and make available every method of treatment that promises to loosen the grip that infantile paralysis has on our children. If, on the basis of tests made, a method is found effective, the full resources of The National Foundation for Infantile Paralysis will be thrown behind it. The one-half million dollars of your money spent on the Kenny method to date certainly proves that.

The National Foundation for Infantile Paralysis is your Foundation—a Foundation dedicated to one purpose and one purpose only—final and complete conquest of infantile paralysis.

Until that conquest is made, the National Foundation will carry on the most ambitious research program ever marshaled against any disease. It will also continue to provide hospitalization and medical care, including the Kenny treatment, in every community to every infantile paralysis victim who needs it. And it will continue to evaluate and aid every new method that is brought to its attention.

It is the people of America who have made all that possible!

—*The National Foundation for Infantile Paralysis, Inc.*  
New York, N. Y.



# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## TERMINAL HEMORRHAGIC SHOCK

### CIRCULATORY DYNAMICS, RECOGNITION, AND TREATMENT

K. G. KOHLSTAEDT, M.D., AND IRVINE H. PAGE, M.D., INDIANAPOLIS, IND.

*(From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital)*

C ONTEMPORARY evidence proves beyond doubt that treatment of early hemorrhagic shock, even when severe, by plasma or whole blood, is most satisfactory. From the practical viewpoint of restoring circulation it is probable that only minor modifications will be made in the near future to improve it. On the other hand, terminal hemorrhagic shock has received much less study and its management can surely be improved. As McMichael puts it, "It seems that under battle conditions this irreversible state may constitute the major problem of shock owing to the unavoidable delays in getting the patient back to base hospitals. The problem is therefore both urgent and practical."

Those of us who have managed only relatively small numbers of major accidents in civilian practice have seen examples of patients in extremis from loss of blood, to whom either plasma could not be administered at all for lack of time or, more commonly, the patient died after the first bit of plasma ran in. It was to study this question that our investigation was undertaken.

To overcome certain of the difficulties of administering plasma or blood by vein when the patient was dying, we investigated, in 1942, the possibility of administering it by artery instead of by vein (Kohlstaedt and Page). This method proved to have advantages. The artery (femoral preferable) can and should be exposed without delay, avoiding the often futile search for collapsed veins. Plasma is administered under a fixed pressure, hence the initial rate of infusion is rapid while the amount infused is automatically controlled by the circulatory system itself. For example, when the pressure is set at 50 mm. Hg, plasma flows in until the pressure in the circulatory system reaches this level. Under this circumstance the arterial pressure is restored more rapidly than when plasma is given by vein so that precious minutes are saved which may spell the difference between success or failure. An additional advantage was found in that about one-half as much plasma was required to restore the circulation as when plasma was given by vein.

We were not convinced at that time that criteria had been found surely indicating lack of survival when all of the blood that had been removed was returned. A few animals survived contrary to predictions based on our criteria. In short, the great individual variations among the animals proved a more and more important handicap as the severity of shock was increased.

From clinical observations we have never been convinced, despite the statement, now almost an aphorism, that shock is wholly peripheral circulatory failure, and its corollary, that the heart is normal in shock. For this reason we sought methods of demonstrating in late shock failure of the heart to perform its functions adequately.

Wiggers and Werle (1942) have recently shown in an important study that after prolonged hemorrhagic hypotension the capacity of the ventricles to respond to a given venous pressure (stretch) is reduced and that this hypodynamic state is masked when venous pressure declines concurrently. Prolonged reduction in coronary flow is suggested as the cause. Their results strongly suggest that reduced capacity of the myocardium to respond to given venous pressures is one of the factors which precipitates an irreversible circulatory state.

In burn shock, study of the circulatory dynamics showed that during the terminal phase the heart as well as the blood vessels became refractory to stimulating drugs (Page). They seemed exhausted. It was not unreasonable to suppose that the same might occur after prolonged hemorrhage, hence we turned to use of the cardiometer as the best method at hand for demonstrating cardiac injury. It has not only supplied us with a criterion for terminal shock but, as a result of study of the sequence of events after hemorrhage, pointed to the needs in treatment of the condition. The study on animals is reported in this communication and the clinical experience will be reported in another.

#### METHODS

Dogs weighing 12 to 20 kg. were not fed for twenty-four hours and then anesthetized by the intraperitoneal injection of 30 mg. per kilogram of sodium pentobarbital. The carotid artery was dissected out and a glass cannula inserted, which was connected by a Y tube to two mercury manometers. One manometer recorded arterial pressure on a slow-moving kymograph which ran continuously during the experiment and the other recorded on a rapidly moving one which was operated at short intervals for the purpose of recording the movements in the cardiometer. A metal cannula was inserted into the trachea for artificial respiration during the period the thoracic cavity was open. A glass cardiometer was placed about the heart through an opening in the chest wall which had been made by careful resection of the left fifth rib. A glass tube was extended from the pleural cavity through the chest wall and then each layer of tissue was sutured around this tube and the stem of the cardiometer. The cardiometer and tube from the pleural cavity were

connected to a differential manometer (Boyd and Patras, 1941)\* and negative pressure was established within the thoracic cavity, cardiometer, and chambers of the differential manometer. (The details of the application and construction of the complete apparatus for use of a cardiometer with a closed chest will be described in a separate communication.)

When negative pressure had been restored, artificial respiration was discontinued and the animal breathed spontaneously. Respirations were recorded on the drum of a kymograph by means of a tambour connected to the tube leading from the pleural cavity. A water manometer was also connected to this tube to measure the intrathoracic pressure. This pressure was maintained at the same level present before the chest was opened. Changes in intrathoracic venous pressure were recorded by inserting a No. 12 rubber catheter down the right external jugular vein until its tip was in, or very near, the right atrium. The catheter was filled with heparin solution and connected to a water manometer. A long shellacked cork served as a float for the manometer and thus it was possible to record changes in venous pressure on the drum.

The femoral vein and artery were dissected out and glass cannulae inserted. The cannula in the femoral artery was connected to the apparatus for withdrawing blood and the vein was connected to the reservoir of this apparatus so that blood could be returned. This apparatus and the method of producing sustained posthemorrhagic hypotension has been described by us (Kohlstaedt and Page, 1943). Ten per cent sodium citrate was used as anticoagulant and great care was exercised in preventing an excess of it in the blood in the reservoir.

#### EFFECT OF PROLONGED POSTHEMORRHAGIC HYPOTENSION ON CIRCULATORY DYNAMICS

The change in stroke-volume, cardiac output, heart size, and venous and arterial pressure which result from intermittent bleeding are schematized in Fig. 1.† The uppermost tracing represents the record from the cardiometer, the upper margin of which records diastolic volume and the lower margin systolic volume. The distance between is equivalent to stroke volume. The next lower tracing represents intrathoracic venous pressure (millimeters of water) and below this is recorded arterial pressure (millimeter of mercury). The vertical dotted lines represent the points at which blood was withdrawn or injected, the

\*We wish to thank Dr. T. E. Boyd for his gracious aid in the construction of the cardiometer.

†The actual values for cardiac output during the course of the experiment which has been schematized in Fig. 1 are: at A, prehemorrhagic control, average stroke volume 16 c.c., heart rate 100 per minute, and cardiac output 1.8 liters per minute. At B, the point of maximum reduction in heart size, the average stroke volume was 5.6 c.c., the rate 150 per minute, and cardiac output 0.8 liter per minute. At C, after considerable cardiac dilatation had occurred and arterial pressure had fallen progressively, average stroke volume was 4 c.c., heart rate 160 per minute, and cardiac output 0.6 liter per minute. At D, after a second injection of 35 c.c. of blood had been given intra-arterially, average stroke volume was 3.6 c.c., heart rate 80 per minute, and cardiac output 0.28 liter per minute. Finally at E, the point of extreme cardiac dilatation and arterial pressure rapidly declining despite a third injection of 35 c.c. of blood intra-arterially, the average stroke volume was 2 c.c., heart rate 100 per minute, and cardiac output 0.3 liter per minute.

amount in cubic centimeters being given at the top of the chart. The total amount of blood removed is indicated by the shaded area at the bottom.

Let us illustrate the course of events by describing a typical experiment. Following the first three hemorrhages, stroke volume, cardiac size (diastolic volume), venous pressure, and arterial pressure all declined sharply to be followed within twenty minutes by a rise in venous and arterial pressure. Stroke volume and cardiac size, however, remained reduced. As the amount of each hemorrhage became smaller, changes in arterial and venous pressure were less pronounced. Heart

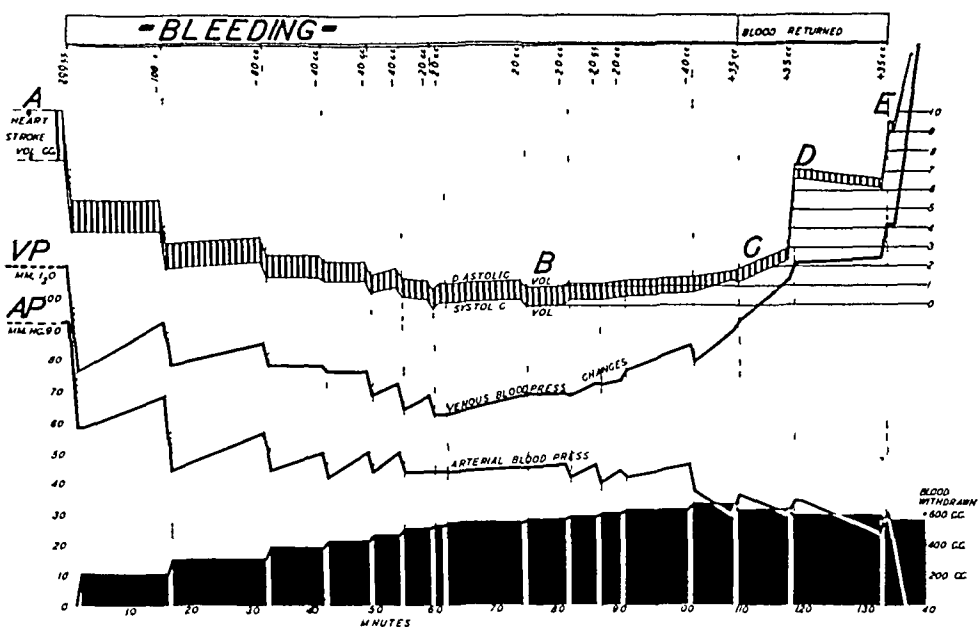


Fig 1—Schematic diagram of the effect of hemorrhage and prolonged hypotension on circulatory dynamics. A, Cardiometer record of stroke volume in prehemorrhagic period. B, Point of greatest reduction of diastolic and systolic volume. C, D, and E, 35 c.c. of blood injected intra-arterially. VP, Intrathoracic venous pressure in millimeters of water. AP, Arterial pressure in millimeters of mercury.

Shaded area denotes total amount of blood removed (scale at right side). Scale at upper right indicates stroke volume units of cardiac dilatation.

size continued to decline until at point B it was minimal. Fixed hypotension was established at 46 mm. Hg. During the twenty minutes of hypotension preceding point B, venous pressure rose steadily and continued to rise in spite of further withdrawal of blood. Five minutes after the maximum decrease in cardiac size had occurred, both systolic and diastolic volume began to increase and this was not affected by further withdrawal of two 20 c.c. and one 40 c.c. portions of blood. The rise in systolic volume was more rapid than rise in diastolic so that stroke volume grew smaller as dilatation progressed. These cardio-dynamic changes were accompanied by marked reduction in heart rate in all experiments. One hundred minutes after the initial bleeding,

following the removal of another 40 c.c. portion of blood, arterial pressure fell precipitously and at *C*, 35 c.c. of blood were returned intra-arterially. A very brief rise in arterial pressure occurred but the rate of cardiac dilatation and increase in venous pressure were not reduced. A second injection of blood at *D* produced even less rise in arterial pressure and was followed by a very marked rise in both systolic and diastolic volume. Cardiac size and venous pressure were maintained for about ten minutes but the arterial pressure declined steadily, and at *E* a third injection of 35 c.c. of blood was given. This was followed by a sharp increase in heart size, concomitant rise in venous pressure, and precipitous decline in arterial pressure. Death ensued at this point.

Similar changes in circulatory dynamics were observed in twenty-seven experiments and the results are shown in Tables I to III. The stroke volume, heart rate, cardiac output, and arterial pressure were recorded at five points in each experiment. These were: I, during the prehemorrhagic period; II, during hypotension, the point at which maximum reduction in cardiac size occurred; III, at the completion of the hypotensive period, that is just before treatment began; IV, immediately after treatment ended; V, after circulation had become stabilized, that is from fifteen to sixty minutes after treatment had been completed. Changes in venous pressure and diastolic volume were measured at points II to V.

The changes which are typical of prolonged posthemorrhagic hypotension are summarized in Table IV.

These changes, as observed in the kymograph record of a typical experiment, are illustrated in Fig. 2. This figure is composed of sections of the record taken at each of the crucial points in an experiment. Section *I* is from the prehemorrhagic period; section *II* was taken 100 minutes later when hypotension had been established and there was a maximum reduction in cardiac size. This is indicated by the decline in systolic volume (lower margin of the cardiometer record) from line *X* to *Y*. The stroke volume had decreased from 13 to 5 c.c., heart rate from 150 to 130, and cardiac output from 2 to 0.6 liters per minute. Venous pressure had declined 5 cm. of water and arterial pressure remained at 40 mm. Hg. The increase in rate and depth of respiration is shown by the uppermost tracing on this record. Hypotension was continued for another twenty-two minutes and the changes which occurred in circulatory dynamics are shown by Section *III* (Fig. 2) at *T*. The increase in cardiac size is indicated by the return of systolic volume to line *X* from line *Y*. Stroke volume declined from 5 to 4.3 c.c., heart rate from 120 to 80 per minute, cardiac output from 0.6 to 0.3 liter per minute. Venous pressure rose 1 cm. of water and arterial pressure declined to 24 mm. Hg. There was a marked decrease in depth and rate of respiration. At *T*, 20 mg. of tuamine were injected. The changes produced will be discussed in another section of this communication.

The time required before cardiac dilatation occurred varied widely and was not correlated with the amount of blood removed. For example, in Exp. 66, Table I, cardiac dilatation did not occur after 185 minutes of hypotension which had been produced by the removal of 530 c.c. of blood (equivalent to 4.6 per cent body weight) but in Exp. 89, Table I, 2.6 stroke volume units of dilatation were present after forty-seven minutes of hypotension, and in Exp. 63, Table I, 105 minutes had elapsed before the same degree of dilatation occurred. Another example of the complete lack of correlation between these factors is found in Exp. 77, Table II, in which a quantity of blood equal to 4.6 per cent of body weight was removed; 125 minutes of hypotension resulted in 1.6 units of dilatation, while in Exp. 99, Table II, the removal of blood equal to 2.2 per cent of body weight, and fifty-seven minutes of hypotension produced 3.2 units of dilatation.

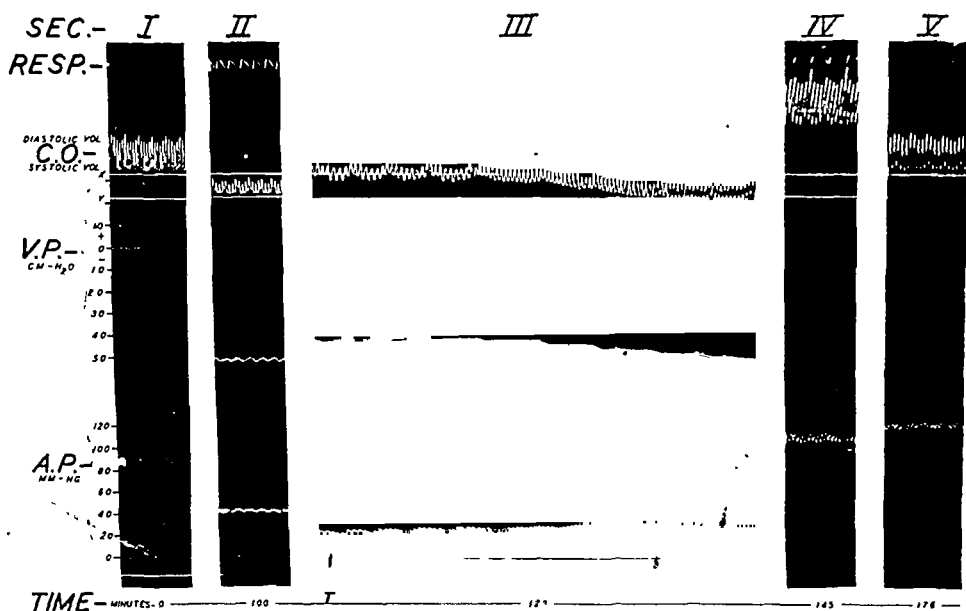


Fig. 2.—Treatment of posthemorrhagic shock after onset of cardiac dilatation by preceding the infusion of blood with the injection of tuamine. *Resp.*, Record of rate and depth of respiration; *CO.*, record of cardiometer; *VP.*, intrathoracic venous pressure in centimeters of water; *AP.*, arterial pressure in millimeters of mercury; *X*, level systolic volume in prehemorrhagic period, and *Y*, level during maximum constriction of heart.

Section I, prehemorrhagic period; Section II, 100 min. later, during hypotensive period when greatest reduction in systolic volume was observed; Section III, 22 min. later in hypotensive period when cardiac dilatation was present; *T*, 20 mg. tuamine; Section IV, immediately after infusion; Section V, 30 min. after. Speed of kymograph, 1.8 cm.  $\equiv$  6 sec.

In eleven experiments the circulation time was measured at intervals during the hypotensive period by the intravenous injection of 0.3 c.c. of a 0.5 per cent solution of NaCN. The results (Table V) indicate that during the state of bleeding the circulation time is prolonged but as hypotension is established it is temporarily improved, that is it is

TABLE  
TREATMENT OF TERMINAL POSTHEMORRHAGIC

EXP. NO.	DOG'S WEIGHT (KG.)	C.C. OF BLOOD REMOVED	BLOOD LOSS $\equiv$ % BODY WEIGHT	DURATION OF HYPOTENSION (IN MIN.)	C.C. OF BLOOD INFUSED	RATE OF INFUSION (C.C./MIN.)	STROKE VOL. (C.C.)					HEART RATE PER MIN.				
							I*	II	III	IV	V	I	II	III	IV	V
66	11 5	530	4 6	185	530	26	9	5	4	14	22	160	110	120	60	70
62	12	465	3 8	137	235	34	28	18	15	22		120	90	100	80	
63	11 2	345	2 6	105	100	35	10	5	4 7	$\pm 2$		120	130	120	70	
69	13 8	600	4 1	112	135	27	14	3 6	5 6	4 1		150	120	160	70	
89	14	300	2 1	47	180	36	9	4 5	5			160	150	80		
90	14	520	3 7	74	160	26	11 5	7 6	7 0	8		150	130	90	50	
76	14	620	4 5	134	none	none	16	5 6	3 3			110	150	80		

Period in experiment at which observation was made.

During prehemorrhagic period; II, point at which maximum reduction in cardiac size occurred during hypotension; III, point just before treatment began after onset of cardiac dilatation; IV, immediately after treatment; V, fifteen to sixty minutes after treatment.

TABLE  
TREATMENT OF TERMINAL POSTHEMORRHAGIC HYPOTENSION BY THE

EXP. NO.	DOG'S WEIGHT (KG.)	C.C. OF BLOOD REMOVED	BLOOD LOSS $\equiv$ % BODY WEIGHT	DURATION OF HYPOTENSION (IN MIN.)	C.C. OF BLOOD INFUSED	RATE OF INFUSION (C.C./MIN.)	AMT. TITANINE (MG./KG.)	STROKE VOL. (C.C.)					HEART RATE PER MIN.				
								I*	II	III	IV	V	I	II	III	IV	V
71	14 3	600	4 2	42	564	40	1 4	20	6 4	5 6	9 1	12	190	160	110	160	160
73	12 5	480	3 9	83	480	34	1 6	18	10	3 7	22	22	130	130	90	100	110
75	11 5	310	2 7	64	310	34	1 7	13	6 3	4 0	19	17	140	150	130	140	130
77	12	550	4 6	125	550	36	1 6	13	5	4 3	8 5	20	150	130	80	100	100
82	12	410	3 4	76	410	20	1 6	7	4 4	4 0	14	12	160	120	50	130	130
99	14	320	2 2	57	320	45	2 1	11 4	7 7	8 3	13 4	11	140	110	70	120	140
101	14	470	3 3	125	470	42	2 0	14 2	7 3	10 4	19	16	140	110	60	110	130
105	11	340	3 0	117	340	42	2 0	14	8 2	8 0	15	12	120	160	130	160	180
106	12 1	435	3 6	100	405	58	2 0	15	7 6	4	24	13	170	150	70	110	110
109	16	640	4 0	65	575	44	2 0	16	7 8	7 2	16	17	170	130	110	150	180

\*Spontaneous breathing stopped.

TABLE  
TREATMENT OF TERMINAL POSTHEMORRHAGIC HYPOTENSION BY THE ADMINISTRATION

EXP. NO.	DOG'S WEIGHT (KG.)	C.C. OF BLOOD REMOVED	BLOOD LOSS $\equiv$ % BODY WEIGHT	DURATION OF HYPOTENSION (IN MIN.)	DRUG USED	AMT. MG./KG.	C.C. OF BLOOD INFUSED	IN-FUSION RATE (C.C./MIN.)	AVERAGE STROKE VOL. (C.C.)					HEART RATE PER MIN.				
									I*	II	III	IV	V	I	II	III	IV	V
84	15 3	400	2 6	53	4-amine	1 9	400	40	12	5	7	19	16	110	120	100	140	150
86	12 0	290	2 4	56	4-amine	2 5	290	20	14	5	5	10	14	130	120	100	100	140
87	13 0	340	2 5	47	4-amine	1 5	150	30	13	4	2			150	120	80		
88	12 0	400	3 3	128	4-amine	2 5	400	36 3	19	4	2 7	24	16	130	140	100	100	110
97	13 5	580	4 2	55	1-amine	2 0	580	29 0	16	5 1	5	14 7		120	170	120	50	
98	15 4	570	3 7	80	1-amine	2 0	80	26 6	14	7 5	7 3			140	150	90		
94	18 0	620	3 2	51	paredrine		580	32	9	4 6	4	11	11	130	120	80	120	140
96	12 3	400	3 2	84	paredrine		none	none	10 5	6 6	3 5			160	120	70		
91	12 5	440	3 5	80	1-10,000 adren.	30 gamma	140	46	10	5 5	8	10		150	140	60	90	
92	12 8	395	3 1	75	1-1,000 adren	1000 gamma	345	38	10	5	$\pm 2$	9		150	170	100	70	

## HYPOTENSION BY INFUSION OF BLOOD ALONE

CARDIAC OUTPUT (l./MIN.)					ARTERIAL PRESSURE (mm. Hg.)					CHANGE VENOUS PRESSURE (cm. H <sub>2</sub> O)				CHANGE DIASTOLIC VOL. (mm.)				IN- CREASE SYS- TOLIC VOL.	STROKE VOL. UNITS	CIRCULATION
I	II	III	IV	V	I	II	III	IV	V	II	III	IV	V	II	III	IV	V			
1 4	0 5	0 5	0 8	1 5	100	42	44	50	84	-4 5	+0 1	+12	-4	-10	+11	+53	-34	none	none	Restored
3 4	1 6	1 5	1 8		100	72	44	36		-5	+1 8	+6		-11	+13	+27		3	0 16	Died
1 2	0 6	0 5	0 14		106	50	40	26		-1 0	+0 8	+4 5		-11	+9			13	2 6	Died
2 2	0 4	0 9	0 3		110	54	42	22		-7 4	+3 7	+11 7		-20	+14	+9		16	4 4	Died
1 4	0 6	0 4			102	40	34	18		-1 2	+0 6	+9 4		-15	+13	+39		12	2 6	Died
1 7	1 0	0 36	0 4		92	40	28	22		-5 0	+1 0			-12	+10	+31		12	1 5	Died
1 8	0 8	0 3			92	38	24			-3 8	+3 2	+2 6		-15	+32				10 5	Died

## II

## ADMINISTRATION OF TUAMINE SULFATE AND INFUSION OF BLOOD

CARDIAC OUTPUT (l./MIN.)					ARTERIAL PRESSURE (mm. Hg.)					CHANGE VENOUS PRESSURE ON WATER				CHANGE DIASTOLIC VOL. (mm.)				EQUIV. SYS- TOLIC VOL. CHANGE III	STROKE VOL. UNITS	CIRCULATION
I	II	III	IV	V	I	II	III	IV	V	II	III	IV	V	II	III	IV	V			
3 8	1 6	0 6	1 4	1 9	138	46	24	78	96	-8	+7	+5	-2	-23	+24	+43	-42	+28	4 3	Restored
2 3	1 3	0 3	2 2	2 4	86	44	24	106	110	-4	+0 1	+6	+4	-4	+10	+30	-12	+10	1 0	Restored
1 8	0 9	0 5	2 6	2 2	96	42	32	120	80	-3	+2 5	+6	+6	-15	+7	+21	-5	+15	2 4	Restored
2 0	0 6	0 3	0 8	2 0	88	42	24	52	118	-6	+2 0	+7 0	-4	-20	+12	+10	-10	+8	1 6	Restored
1 1	0 5	0 2	1 8	1 5	112	58	32	110	124	-4 3	+12	-5	-9	-14	+43	-15	-23	+50	11 3	Restored†
1 6	0 8	0 6	1 6	1 5	98	46	20	150	118	-12	+1 1	+11	-8 8	-10	+22	+28	-20	+25	3 2	Restored
2 0	0 8	0 6	2 1	2 1	104	48	30	100	98	-4 5	+3 6	+6 5	-4 5	-13	+15	+35	-33	+15	2 0	Restored†
1 7	1 3	1 0	2 5	2 1	82	42	20	80	90	-1 9	+0 7	+4 3	-1 9	-22	+14	+4	-7	+7	0 85	Restored†
2 5	1 1	0 3	2 6	1 4	110	42	20	118	114	-3 4	+2 4	+1	-6	-25	+21	+54	-32	+28	3 7	Restored†
2 7	1 0	0 8	2 4	3 0	126	42	30	118	100	-7	+2 3	+10 8	-5 3	-22	+20	+35	-32	+26	3 3	Restored†

## III

## OF ONEAMINE, FOURAMINE, PAREDRINE, ADRENALIN AND INFUSION OF BLOOD

CARDIAC OUTPUT (l./MIN.)					ARTERIAL PRESSURE (mm. Hg.)					CHANGE VENOUS PRESSURE (cm. H <sub>2</sub> O)				CHANGE DIASTOLIC VOL. (mm.)				IN- CREASE SYS- TOLIC VOL. (PER MIN.)	STROKE VOL. UNITS	CIRCULATION
I	II	III	IV	V	I	II	III	IV	V	II	III	IV	V	II	III	IV	V			
1 3	0 6	0 7	2 6	2 4	140	70	50	142	150	-4	+8	-0 5	-2 5	-21	+27	-4	-1 4	25	3 5	Restored
1 8	0 6	0 5	1 0	1 96	80	30	28	72	86	-7	+4	-3	-1	-30	+21	-8	-5	17	3 4	Restored
1 5	0 5	0 16		1	98	38	26			-2	+1 7	+3		-5	+10			20	5 0	Died
2 4	0 5	0 27	2 4	1 76	92	38	28	160	120	-4	+1	+10	-3	-28	+16	+10	-6	12	3 0	Restored
2 0	0 87	0 6	0 73		110	50	38	46		-5 4	+4 2	+12		-44	+9	+37		13	2 5	Died
1 96	1 13	0 6			102	42	30			-5 2	+2 8			-21	+23			25	3 3	Died
1 2	0 56	0 3	1 3	1 5	118	46	34	120	120	-4	+1 6	+5 8	+3	-23	+13	+3	+10	16	3 47	Restored
1 7	0 8	0 24			84	40	22			-1 5	+1 9			-6	+4			11	1 6	Died
1 5	0 8	0 5	0 9		86	42	30	30		-3 4	+2 6	+4 8		-12	+10	+8		10	1 8	Died
1 5	0 85	0 2	0 63		90	44	28	30		-23	+7	+9		-8	+16	+7		25	5 0	Died



TABLE IV

CHANGE IN:	FROM PREHEMORRHAGIC STATE (I) TO THE POINT DURING HYPOTENSION AT WHICH MAXIMUM REDUCTION IN CARDIAC SIZE APPEARED (II)	FROM POINT II TO END OF HYPOTENSIVE PERIOD (AFTER CARDIAC DILATA- TION, III)
Stroke volume	Decreased, average 51 per cent	20 decreased 6 increased Mean, 9 per cent
Heart rate	In 16 decreased In 10 increased	25 decreased 1 slight increase
Cardiac output	Decreased, average 54 per cent	Decreased, average 31 per cent
Venous pressure	Decreased, average 4.4 cm. H <sub>2</sub> O	Increased, average +2.7 cm. H <sub>2</sub> O
Diastolic volume (Cardiometer record)	Decreased, average 17 mm.	Increased, average +16 mm.

shortened. However, as cardiac dilatation appears and venous pressure rises, the circulation time again grows longer.

Treatment by intravenous infusion of all of the blood removed was uniformly successful and easily accomplished provided the infusion was begun before the onset of cardiac dilatation (point *B*, Fig. 1 or Section *II*, Fig. 2). If the infusion was delayed until onset of cardiac dilatation (Section *III*, Fig. 2) it was seldom successful and the animal succumbed before it could be completed. It was, therefore, obvious that before undertaking a comparative study of different agents for the treatment of the terminal stage of hemorrhagic shock, it was imperative that a satisfactory criterion for estimating the effect of hypotension on the cardiovascular system be established.

#### SELECTION OF A CRITERION FOR ESTIMATING SEVERITY OF SHOCK

Criteria such as withdrawal of a specified quantity of blood, reduction of arterial pressure to a fixed level, and maintenance of the pressure at this level for a certain length of time have proved in our experience to be inadequate because some animals can tolerate blood loss and hypotension much better than others.

In our previous study in which the intra-arterial infusion was compared with the intravenous method (Kohlstaedt and Page, 1943) the lack of pressor response to 0.3 c.c. of 1:10,000 adrenalin was used as a criterion but in these experiments some of the dogs could be saved by the intravenous infusion of all of the blood that had been withdrawn. The most that could be said was that refractoriness to the pressor effects of adrenalin greatly jeopardized the chances of survival after transfusion. Therefore this criterion could not be used for our present study because we wished to continue hypotension in *all* experiments until the animal could no longer be saved by the intravenous infusion of blood.

Another criterion of irreversible shock which has been used by some investigators in recent studies is the absence of a pressor response to

TABLE V  
EFFECT OF POSTHEMORRHAGIC HYPOTENSION ON CIRCULATION TIME

EXP. NO.	PREHEMORRHAGIC PERIOD				SOON AFTER BLEEDING				HYPOTENSIVE PERIOD				TERMINAL PHASE—CARDIAC DILATATION PRESENT				AFTER TREATMENT—CIRCULATION RESTORED			
	ART. PRES. (MM. HG)	C. O. (L. PER MIN.)	CIRCULATION TIME (IN SEC.)	DURATION OF HYPO-TENSION (IN MIN.)	ARTERIAL PRESSURE (MM. HG)	C. O. (L. PER MIN.)	CIRCULATION TIME (IN SEC.)	DURATION OF HYPO-TENSION (IN MIN.)	ART. PRES. (MM. HG)	C. O. (L. PER MIN.)	CIRCULATION TIME (IN SEC.)	DURATION OF HYPO-TENSION (IN MIN.)	ARTERIAL PRESSURE (MM. HG)	C. O. (L. PER MIN.)	CIRCULATION TIME (IN SECONDS)	ARTERIAL PRESSURE (MM. HG)	C. O. (L. PER MIN.)	CIRCULATION TIME (IN SEC.)		
62	100	3.4	16	14	72	1.6	28	31	44	1.8	24	135	36	1.8	29	96	1.9	16		
63	106	1.2	30	26	50	0.6	64	102	40	0.6	60	133	42	0.7	40	106	2.2	15		
64	132	1.3	24	38	54	0.56	50	71	40	0.63	36									
66	100	1.4	17	55	42	0.5	43	181	44	0.5	29	235	30	0.6	68					
68	84	1.2	11	6	38	0.98	25	52	38	0.7	23	89	38	0.9	26					
69	110	2.2	14	19	48	0.8	71	54	42	0.9	51									
70	90	2.5	18	33	42	1.4	66	38	42	1.2	58									
71	138	3.3	24	6	46	1.3	27	25	40	0.6	31									
73	80	2.6	16	7	44	1.4	21	45	38	1.0	27	72	30	0.6	37					
74	108	3.0	18.3	14	42	1.7	20	55	38	1.5	16	82	36	0.9	25					
67	118	2.2	21	45	40	0.5	43	60	46	0.8	30	123	42	0.9	37					

the injection of 2.5 c.c. per kilogram of whole blood. However, we were able to save some dogs after the requirements of this criterion had been fulfilled. Furthermore, in some experiments the hypotensive period was continued for fifteen or twenty minutes after a test dose of blood failed to give a pressor response and at the end of this time the injection of blood was repeated. The second injection produced a rise in arterial pressure although the initial injection had failed.

We had observed that stroke volume in most instances of very severe shock was reduced about 70 per cent; hence, an attempt was made to use this as a criterion, but it too was unsatisfactory, because in five experiments in which it had been reduced an average of 64 per cent, normal circulation was restored by intravenous administration of citrated whole blood.

Another observation was that the intravenous method of readministering blood *never failed* if treatment was begun before the phase of cardiac dilatation occurred. If hypotension was continued until *slight* cardiac dilatation had occurred, then the administration of blood was an inadequate form of treatment.

From this observation it was evident that the degree of cardiac dilatation might serve as a criterion for the stage of shock not successfully treated by infusion of blood alone. If the criterion was to be useful, some method was necessary for expressing the amount of dilatation present at the time treatment was instituted. For this purpose we employed as a unit the *height* of the cardiometer tracing, that is the stroke volume, at that period in the experiment when cardiac dilatation could first be detected (*B*, Fig. 1). The distance is measured from the lower margin of the cardiometer tracing to a base line established by extending a line from the level of systolic volume at the time cardiac dilatation begins. When the lower margin has risen to a point which is equal to the height of the stroke volume, one unit of dilatation has occurred. This is illustrated in Fig. 1. The scale along the right margin of the cardiometer tracing refers to units of cardiac dilatation. At *C* two units of cardiac dilatation are represented, at *D*, seven units, and at *E*, ten units.

The following illustrates the use of stroke volume units. In Exp. 76, Table I, no attempt was made to treat the dog, and it died when cardiac dilatation reached 10 stroke volume units. In Exp. 82, Table II, the dog received 20 mg. of tuamine prior to the infusion of 410 c.c. of blood, when cardiac dilatation was also 10 units, but normal circulation was restored.

#### CARDIODYNAMIC EFFECT OF DRUGS BEFORE AND AFTER HEMORRHAGE

The evidence presented suggests that a drug to be useful in the terminal phase of hemorrhagic shock must have at least the following properties: (1) it must increase cardiac output; (2) it must decrease cardiac dilatation; (3) it must cause a minimal increase in peripheral

resistance; and (4) its action must be of such duration that if an intravenous infusion is begun simultaneously, a quantity of blood sufficient to restore the circulation can be given during the period the drug is acting.

Decrease in diastolic volume is essential because cardiac dilatation has already begun in the terminal phase and the intravenous infusion of blood will of itself tend to increase further the heart size; therefore, the drug selected should be one which would counteract this effect. It must not increase peripheral resistance proportionately more than cardiac output. In the terminal phase there is already increased peripheral resistance and the more this is increased the more difficult it will be for the heart to maintain adequate circulation. By comparing the change in cardiac output with the rise in arterial pressure, the change in peripheral resistance which a drug produces can be estimated. Thus, a drug which causes a large rise in arterial pressure with a minimal change in cardiac output acts primarily on the peripheral vessels, whereas one that causes a smaller rise in arterial pressure and much larger changes in cardiac output must have a primary cardiac action.

With these thoughts in mind a search was made for a quick acting drug which would have a primary cardiac action.

*Methyl iso-thiourea*.—Methyl iso-thiourea was studied because it had been used by McGeorge<sup>6</sup>, Sherif, and Smirk (1942) in the treatment of traumatic shock in animals. It was injected intravenously into ten normal and five hypotensive dogs (Table VI). The amount given varied from 10 mg. per kilogram to 1.4 mg. per kilogram. In normal dogs the effect on stroke volume was equivocal; it reduced it in five and increased it in the other five. The change varied from a 66 per cent increase to 36 per cent decrease. The heart rate was decreased in all of the normal dogs, the minimum being 7 per cent and the maximum 50 per cent. These changes in stroke volume and rate could not be correlated with the amount of drug given. For example, the same increase in stroke volume and reduction in heart rate was produced by 1.4 mg. per kilogram used in Exp. 55 (Table VI) as had been obtained when 9 mg. per kilogram had been given in Exp. 41 (Table VI).

The cardiac output per minute was decreased in nine of the ten experiments because in all but two (Exp. 36 and 58, Table VI) in which stroke volume increased, the increase was not large enough to compensate for the reduction in heart rate. The reduction in cardiac output also bore no relation to the amount of drug used.

The rise in arterial pressure varied markedly and could not be correlated with the amount of drug administered (Table VI). A handicap limiting its usefulness is the fact that after two or three injections the animal's pressor response is progressively converted to a depressor one.

Methyl iso-thiourea caused an increase in diastolic volume in nine of ten normal dogs. Expressed in stroke volume units, the greatest dila-

TABLE VI  
CIRCULATORY DYNAMIC EFFECTS OF METHYL ISO-THIOUREA BEFORE AND AFTER HEMORRHAGE

EXP. NO.	DOG	(WEIGHT IN KG.)	DOSE (MG. PER KG.)	STROKE VOL.			HEART RATE			CARDIAC OUTPUT (L. PER MIN.)			ARTERIAL PRESSURE (MM. HG.)				CHANGE VENOUS PRESSURE (C.V. WATER)	CAR. DIL. (STROKE VOL. UNITS)	C.C. OF BLOOD REMOVED	BLOOD LOSS PER % B.W.	HYPOTEM. (IN MIN.)
				BEFORE DRUG		% CHANGE	BEFORE DRUG		% CHANGE	BEFORE DRUG		% CHANGE	BEFORE DRUG		% CHANGE						
				BEFORE DRUG	AFTER DRUG	BEFORE DRUG	AFTER DRUG	BEFORE DRUG	AFTER DRUG	BEFORE DRUG	AFTER DRUG	BEFORE DRUG	AFTER DRUG	BEFORE DRUG	AFTER DRUG						
<i>Before Bleeding</i>																					
36	15		0.10	6.2	10.3	+66	150	110	-27	0.9	1.13	+21	90	132	42	+46	+3.5	+2.0			
37	20.3	7.3	25	21	-16	150	140	-7	3.7	3.0	-21	78	120	42	+53	None	+0.4				
38	21.6	7.0	14	11	-21.7	130	120	-8	1.8	1.3	-28	130	156	26	+26	-1.0	+0.35				
40	18.3	8.0	14	15	+5	170	140	-18	2.4	2.1	-13	100	132	32	+32	+1.0	+1.0				
41	16.7	9.0	15	21	+36	160	80	-50	2.5	1.7	-32	126	208	82	+65	+4.5	+1.4				
42	20.3	9.8	16	12	-16	140	150	-22	2.3	1.8	-6	86	138	52	+60	-1.4	-1.0				
55	17.7	1.4	14	19	+35	130	70	-46	1.8	1.36	-26	124	136	12	+9	None	+1.07				
56	13.5	7.4	15	10	-33.3	150	120	-33	2.2	1.2	-46	138	202	64	+46	+1.9	+0.3				
57	18	2.7	21	17	-20	190	180	-6	4.0	3	-23	90	138	48	+53	+0.5	+0.3				
58	16	3.1	16	19	+22	160	130	-19	2.5	2.5	None	102	130	28	+27	None	+0.6				
<i>After Bleeding</i>																					
32	22.5	6.6	8	9	+12	160	140	-12.1	1.28	1.26	-2	48	106	58	+120	None	None	950	4.2	37	
35	16.4	9.0	3.5	6.5	+85	130	100	-24	0.36	0.65	+80	40	100	60	+150	None	-2.0	410	2.5	60	
37	20.3	7.2	7	9.2	+31	140	120	-15	0.98	1.10	+12	50	78	28	+36	None	+1.4	670	3.3	19	
38	21.6	7.0	9.0	11.3	+25	160	120	-25	1.4	1.34	-5	50	90	40	+80	+0.2	+0.8	650	3.0	30	
40	18.3	8.2	9.0	10.5	+16	170	160	-6	1.5	1.68	+9	54	110	56	+101	-0.3	None	300	1.6	8	
42	20.3	9.8	11.7	12	+3	150	140	-7	1.7	1.7	None	54	80	26	+48	None	+0.25	400	1.9	13	

tation was 2 and the smallest was 0.3. Again it is interesting to note that the smallest dose used (Exp. 55, Table VI) produced as much, or more, cardiac dilatation than occurred in other experiments in which much larger amounts of the drug were given. The effect on venous pressure was not significant.

In the hypotensive dogs, a more uniform dose was given. It varied from 6.6 to 9.8 mg. per kilogram. The stroke volume increased in all, varying widely from +3 to +85 per cent. Heart rate invariably decreased and in three of the five hypotensive dogs the increase in stroke volume was enough to offset the decreased rate with the result that cardiac output increased.

The pressor effect of the drug was comparable to that in normal dogs. The effect on diastolic volume was much less pronounced than had been observed in normal dogs. In only one animal (Exp. 35, Table VI) was heart size reduced. In two there was no change, in two others there was a moderate increase, and in one there was a large increase (1.4 units). Little change in venous pressure occurred.

*Mixture of Pitressin and Ephedrine.*—A mixture of pitressin and ephedrine has been recommended for use in the treatment of shock by Bourne (1939) and Melville (1932). It was given to five normal dogs and four hypotensive animals (Table VII). In three experiments a dose of  $\frac{3}{16}$  gr. of ephedrine and  $2\frac{1}{2}$  units of pitressin was used, and in the remaining six experiments  $\frac{3}{32}$  gr. of ephedrine and  $1\frac{1}{4}$  units of pitressin.

In four of the normal dogs the mixture produced a decrease in stroke volume and in one an increase. Likewise, in four of five dogs heart rate was decreased and in one it was slightly increased. In all of the normal dogs cardiac output per minute was decreased from 20 to 38 per cent in four dogs, and 71 per cent in the fifth.

The mixture had a moderate pressor action averaging 40 mm. Hg. It produced an increase in heart size in four of the five dogs varying from 0.84 stroke volume units to 1.7 units. A definite rise in venous pressure occurred in four of five dogs, the maximum rise being 3.6 cm. of water. The fifth dog (Exp. 39, Table VII) showed no change.

After bleeding, the effect on stroke volume was equivocal. The maximum increase was 50 per cent and the maximum decrease 49 per cent. Heart rate was reduced in three of four dogs. The effect on cardiac output was slight in two experiments, and was decreased in the other two about 50 per cent. The pressor effect was less than it had been in the normotensive dogs. Cardiac size was increased in all the experiments, the amount being definitely more than it had been in the normal dogs. The largest increase was 3.4 units and this occurred after 460 c.c. of blood had been removed (Exp. 42, Table VI), and hypotension had been present forty-five minutes. Venous pressure increased significantly in all of the hypotensive dogs.

TABLE VII  
CIRCULATORY DYNAMIC EFFECTS OF A MIXTURE OF PITRESSIN AND EPINEPHRINE BEFORE AND AFTER HEMORRHAGE

EXP. NO.	DOG (WT. IN KG.)	DOSE		STROKE VOL.			HEART RATE			CARDIAC OUTPUT (L. PER MIN.)			ARTERIAL PRESSURE (MM. HG)				CHANGE IN VENOUS PRES- SURE (CM. OF WATER)	CAR. DIL. (STROKE VOL. UNITS)	C.C. OF BLOOD REMOVED	BLOOD LOSS PER % B. W.	DURATION OF HYPOTEN- SION (IN MIN.)
		GR.	UNITS	BEFORE DRUG	AFTER DRUG	% CHANGE	BEFORE DRUG	AFTER DRUG	% CHANGE	BEFORE DRUG	AFTER DRUG	RISE	% CHANGE								
<i>Before Bleeding</i>																					
39	22	$\frac{3}{16}$	$2\frac{1}{2}$	7.4	6.3	-15	120	110	-9	0.8	0.6	-22	148	198	50	+33	None	+1.3			
40	18.3	$\frac{3}{32}$	$1\frac{1}{4}$	8.8	12.5	+42	170	100	-42	1.5	1.2	-20	132	160	28	+21	+2.0	+1.02			
41	16.7	$\frac{3}{32}$	$1\frac{1}{4}$	17.6	13.5	-24	140	110	-22	2.38	1.4	-38	114	190	76	+66	+2.0	None			
55	17.7	$\frac{3}{32}$	$1\frac{1}{4}$	13.6	11.7	-14	130	110	-15	1.76	1.28	-28	122	130	8	+6	+3.6	+1.7			
56	13.5	$\frac{3}{32}$	$1\frac{1}{4}$	19	5	-73	130	140	+7	2.4	0.7	-71	118	160	42	+35	+1.7	+0.84			
<i>After Bleeding</i>																					
29	17.4	$\frac{3}{16}$	$2\frac{1}{2}$	6.7	9.0	+50	200	160	-20	1.34	1.4	+4	36	54	18	+30	+2.0	+1.5	600	3.4	30
40	18.3	$\frac{3}{32}$	$1\frac{1}{4}$	9.4	4.8	-49	130	130	None	1.2	0.6	-50	58	76	18	+30	+2.0	+1.7	350	1.9	33
41	16.7	$\frac{3}{32}$	$1\frac{1}{4}$	4.0	4.9	+25	200	160	-20	0.78	0.78	None	64	84	20	+31	+1.6	+2.2	540	3.2	15
42	20.3	$\frac{3}{16}$	$2\frac{1}{2}$	11	7	-37	140	90	-36	1.5	0.6	-60	56	80	24	+42	+3.6	+3.4	460	2.3	45

TABLE VIII

CIRCULATORY DYNAMIC EFFECTS OF ANGIOTONIN BEFORE AND AFTER HEMORRHAGE AND THE EFFECT OF PAREDRINE IN NORMAL DOGS

EXP. NO.	DOG (WT. IN KG.)	DOSE (C.C.)	STROKE VOL. (C.C. PER MIN.)			HEART RATE PER MIN.			CARDIAC OUTPUT (L. PER MIN.)			ARTERIAL PRESSURE (MM. HG)			CHANGE IN VENOUS PRES- SURE (CM. OF WATER)	CAR. DIL. (STROKE VOL. UNITS)	C.C. OF BLOOD REMOVED	BLOOD LOSS PER % B. W.	DURATION OF HYPOTEN- SION (IN MIN.)
			BEFORE DRUG	AFTER DRUG	% CHANGE	BEFORE DRUG	AFTER DRUG	% CHANGE	BEFORE DRUG	AFTER DRUG	% CHANGE	RISE	% CHANGE						
<i>Before Bleeding</i>																			
30		5	21	18	-15	150	150	None	3.1	2.7	- 13	100	140	40	+40	None	+0.2		
31	14	5	21	24	+14	170	160	-6	3.4	3.8	+ 11	90	118	28	+31	+0.5	+0.2		
42	20.3	5	26	25.8	- 1.2	160	160	None	4.1	4.01	- 4	70	102	28	+27	+1.0	+0.2		
56	13.5	5	19	14	-27	150	120	-20	2.8	1.6	- 41	114	164	50	+43	+1.3	+0.4		
57	18	4	17	11	-36	160	160	None	2.7	1.7	- 39	98	122	34	+28	None	+0.7		
58	16	3.5	16	14	-15.7	150	130	-14	2.5	1.8	- 38	90	122	28	+31	+0.9	+0.7		
<i>After Bleeding</i>																			
42	20.3	5	8.4	9.6	+13	110	120	+ 9	0.9	1.15	+ 23	52	68	16	+30	+0.7	+1.07	185	2.3
56	13.5	5	4	5.2	+30	140	130	- 7.2	0.57	0.68	+ 19	52	98	46	+88	+1.7	+3.7	425	3.1
40	18.3	5	9	9.2	+14	160	140		1.4	1.38	- 3.2	58	68	10	+17	+1.0	+1.2	400	2.1
<i>Paredrine (1 Per Cent Solution) Before Bleeding</i>																			
37	18	1.0	19	29	+52	160	230	+43	3	6.6	+120	106	160	54	+50	+1.2	-1.05		
58	16	1.0	12.3	19	+54	160	190	+18	1.9	3.6	+ 89	72	120	48	+66	-1.4	-2.68		



*Angiotonin*.—Six normal dogs received a quantity of angiotonin equivalent in pressor action to 0.5 c.c. of 1:10,000 adrenalin (Table VIII). Stroke volume decreased in five of six dogs; heart rate remained unchanged in three, and decreased in three.

In three hypotensive animals (Table VIII) stroke volume increased, varying from 13 to 30 per cent. Heart rate increased slightly in one and decreased in two. These changes produced concomitant change in cardiac output. The pressor effect was less in the hypotensive dogs than it had been in the normal. A striking effect of angiotonin was that it caused a pronounced increase in diastolic volume when given after bleeding. In Exp. 56 (Table VIII) the increase was 3.7 stroke volume units; in Exp. 42, 1.07 units, and in Exp. 40, 1.2 units (Table VIII). Venous pressure increased in all of the hypotensive dogs. The rise was larger than it had been in the normal dogs.

*Paredrine* (p-hydroxy-a-methyl phenethylaminehydrobromide).—One cubic centimeter of 1 per cent paredrine was administered to two normal dogs. Stroke volume increased 50 per cent; heart rate increased and the result was a large increase in cardiac output. In both dogs arterial pressure increased almost 50 mm. Hg. The most striking effect produced was a decrease in the diastolic volume. The heart size decreased 1 and 2.6 units. This change in diastolic volume is greater and more prolonged than any previously observed. The effect on venous pressure was equivocal.

*Neosynephrin* (levo-a-hydroxy-b-methylamino-3-hydroxy ethylbenzene hydrochloride).—Neosynephrin was administered in varying doses to ten normal dogs, and to eight after hypotension (Table IX).

The effect on stroke volume in normal dogs varied widely. In six dogs it increased; the maximum being 39 per cent. In one dog (Exp. 36, Table IX) it was unchanged, and in three it was reduced. The maximum reduction was 27 per cent. These changes bore no relationship to the amount of drug given. Heart rate decreased an average of 16 per cent in nine of the ten dogs and remained unchanged in one. In only one experiment was the increase in stroke volume of sufficient magnitude to compensate for the decrease in heart rate and here (Exp. 35, Table IX) it was increased 16 per cent. The average rise in arterial pressure in normotensive dogs was 46 mm. Hg. Neosynephrin had only a slight effect on diastolic volume in these animals. Heart size was not altered in four and was increased in six dogs. The maximum increase was 1.4 units. Venous pressure increased to a variable extent in seven and was not changed in three.

The drug was administered to eight hypotensive dogs. The amount varied from 0.1 to 0.5 c.c. of 1 per cent solution of neosynephrin. The effect on stroke volume was extremely variable, ranging from an increase of 100 per cent (Exp. 35, Table IX) to a decrease of 30 per



unchanged in one. The chief difference observed in the action of adrenalin in normotensive dogs and hypotensive dogs was that in the former the average increase in cardiac output was 41 per cent and in the latter 16 per cent. The rise in arterial pressure was about equal in both groups. In both normotensive and hypotensive, diastolic volume was decreased. Changes in venous pressure were variable and were not significant.

*Tuamine* (2-amino heptane sulfate<sup>4</sup>).—The cardiac action of tuamine was tested in ten normal and eight hypotensive dogs. The amount given varied from 0.45 to 1.1 mg. per kilogram. In normal dogs it had a varied effect on stroke volume (Table XI). In six dogs it was reduced an average of 31 per cent, in two it increased 57 per cent in one and 19 per cent in the other, and in two it was unchanged. Heart rate increased in five dogs and decreased in five. The maximum increase was 55 per cent and decrease 31 per cent. In six animals cardiac output was decreased, the maximum being 36 per cent; in one it was unchanged, and in three increased, the maximum being 29 per cent.

The pressor effect as compared to the cardiac action was less marked than that of the other substances tested and it could not be correlated with the amount given. In Exp. 56 (Table XI) in which 1.1 mg. per kilogram was administered, arterial pressure increased 12 mm. Hg., while in Exp. 33 with 0.45 mg. per kilogram), the response was 20 mm. Hg. Diastolic volume decreased in seven of the ten normal dogs, the maximum being 1.8 units (Table XI). A small increase occurred in three experiments. Large but variable changes occurred in venous pressure; in four dogs it declined about 2 cm. of water and in three increased 1.0 cm. These changes also bore no relation to size of the dose. In the hypotensive dogs the drug usually produced a striking increase in stroke volume, while in the normal animals it was increased in only two of the ten dogs. The change was proportionately much greater than in normal dogs (Table XI). In Exp. 36 (Table XI), for example, stroke volume increased 140 per cent. The effect of tuamine on heart rate was just as variable in the hypotensive as in normal dogs. However, the consistently large increase in stroke volume was sufficient to compensate for decrease in heart rate in all but one of eight hypotensive dogs resulting in increased cardiac output in seven dogs.

The pressor effect was similar to that observed in normal dogs, and it was significant that in those experiments in which there had been a great increase in stroke volume and cardiac output (Exp. 29, 31, and 32) the pressor response was smaller than in Exp. 42 in which stroke volume decreased, or Exp. 35 in which cardiac output diminished. Diastolic volume was decreased in six of eight hypotensive dogs. This decrease in cardiac size was definite, the maximum being 3.3 units, the

<sup>4</sup>Eli Lilly and Company.

TABLE XI  
CIRCULATORY DYNAMIC EFFECTS OF TUAMINE SULFATE BEFORE AND AFTER HEMORRHAGE

CIRCULATORY DYNAMIC EFFECTS OF 1-AMINOL SULFATE DERIVATIVES

EXP. NO.	DOG'S WT. (IN KG.)	DOSE OF DRUG (MG. PER KG.)	STROKE VOL.		HEART RATE PER MIN.		CARDIAC OUTPUT (L. PER MIN.)		ARTERIAL PRESSURE (MM. HG)				CHANGE DIASTOLIC VOL. (MILKOE VOL. UNITS)	CHANGE VENOUS PRESSURE (CM. OF WATER)	C.C. BLOOD REMOVED	BLOOD LOSS III PER % B. W.	DEFLECTION OF HYPO-TENSION	
			BEFORE DRUG	AFTER DRUG	% CHANGE	BEFORE DRUG	AFTER DRUG	% CHANGE	BEFORE DRUG	AFTER DRUG	% CHANGE	RISE						% CHANGE
<i>Before Bleeding</i>																		
32	22.0	0.68	20.0	9.0	- 55	130	200	+53	2.6	1.8	36	38	-1.0	+1.0				
33	22.0	0.45	18.0	10.0	- 45	160	180	+12	2.8	1.8	36	16	-0.3	+1.2				
34	20.0	0.75	21.0	17.0	-19	140	170	+21	3.0	3.0	31	29	-0.71	-0.6				
35	16.0	0.93	14.0	11.7	-17	90	140	+55	1.26	1.6	29	76	-1.0	-2.0				
36	15.0	1.0	10.0	6.0	- 40	120	150	+25	1.2	0.9	44	57	-1.0	-2.0				
41	16.7	0.89	15.1	18.0	+19	150	110	-22	2.26	2.0	12	126	-0.26	+1.0				
55	17.0	0.88	19.0	30.0	+57	110	90	-18	2.1	2.7	28	110	+0.15	-1.8				
56	13.5	1.1	17.0	15.0	-12	130	120	-20	2.5	1.9	14	122	+0.17	-2.3				
57	18.0	0.83	12.0	12.0	None	180	150	-17	2.2	1.9	14	152	+0.25	-1.0				
58	16.0	0.93	17.0	17.0	None	160	110	-31	2.7	1.7	26	112	-0.41	None				
<i>After Bleeding</i>																		
29	17.0	0.58	4.4	10.0	+127	210	240	None	1.05	2.4	44	15	-1.4	+1.3	600	3.4	11	
31	19.0	0.78	7.0	11.0	+57	140	170	+21	0.98	1.87	51	16	-3.3	+1.0	450	2.4	29	
32	22.0	0.68	6.0	8.0	+33	220	220	None	1.3	1.7	58	38	-0.8	None	950	4.2	5	
33	22.0	0.45	5.0	5.8	+16	140	150	+7	0.87	0.93	66	63	-3.0	+0.7	350	1.5	4	
35	16.0	0.93	5.3	4.9	- 8	110	140	+27	0.58	0.7	78	56	-3.0	+0.7	360	2.4	35	
36	15.0	1.0	4.0	10.0	+110	110	70	-37	0.45	0.7	80	30	-1.2	None	300	2.0	20	
42	20.0	1.0	9.0	9.8	+ 8	110	100	-10	1.0	0.98	90	37	None	-2.0	460	2.3	25	
56	13.5	1.1	6.2	8.3	+33	140	130	- 8	0.86	1.07	92	61	-0.5	+1.0	425	3.1	95	

minimum 0.5 units. This change could not be correlated with the quantity of tuamine administered. Venous pressure changed variably but in all experiments in which diastolic volume decreased the venous pressure increased.

On the basis of these results tuamine, adrenalin, and paredrine were the only drugs of those tested that possessed the properties which would make them useful in the preinfusion treatment of hemorrhagic shock.

Methyl isó-thiourea was rejected because it did not decrease, but slightly increased, diastolic volume. And the fact that it produced a reduced pressor response or even a depressor one, after a second or third injection, limited its usefulness. The mixture of ephedrine and pitressin was unsatisfactory because it increased diastolic volume. Angiotonin also increased diastolic volume and temporarily reduced cardiac output. Furthermore, the supply of this substance is limited at present. Neosynephrin produced a large rise in arterial pressure and only minor changes in cardiac output, which was indicative of increase in peripheral resistance. In terminal posthemorrhagic shock an increase in the already excessive peripheral resistance might be harmful.

Tuamine decreased diastolic volume to a marked degree in hypotensive animals. The equally consistent increase in cardiac output together with a relatively small rise in arterial pressure suggested that it did not greatly increase peripheral resistance. Paredrine appeared to have the same effect although in two dogs the pressor response was more pronounced than that produced by tuamine. Adrenalin increased cardiac output and decreased diastolic volume, but its action was very brief. Furthermore, it has been established (Kohlstaedt and Page) that the action of adrenalin decreases as the duration of hypotension is prolonged and it would be less effective in the terminal phase of post-hemorrhagic hypotension than tuamine or paredrine.

#### TREATMENT OF TERMINAL POSTHEMORRHAGIC HYPOTENSION BY INFUSION OF BLOOD ALONE

Before undertaking a study of the efficacy of the treatment of severe hemorrhagic shock by administration of a drug prior to the infusion of blood, it was essential that the limitations of the treatment of this degree of shock by the infusion of blood alone should be established. For this purpose five dogs in various grades of severe shock, as determined by the criterion of cardiac dilatation, were treated by infusion of blood alone.

In one animal (Exp. 66, Table I) treatment was started before cardiac dilatation had appeared although the amount of blood removed equalled 4.6 per cent of body weight and hypotension had existed 185 minutes. The intravenous infusion was begun at the rate of 26 c.c. per minute. Venous pressure rose 12 cm. of water and the cardiometer record of diastolic volume rose 53 mm. Stroke volume in-

creased from 4 to 14 c.c. and heart rate decreased from 120 to 60 per minute. Thus, cardiac output was increased from 0.48 liter per minute to 0.84 liter per minute, but arterial pressure increased only 6 mm. Hg during infusion. One hour later circulation was normal, stroke volume having increased to 22 c.c., heart rate to 70, cardiac output to 1.5 liters per minute, and arterial pressure 84 mm. Hg.

In the remaining five experiments of this group (Exp. 62, 63, 69, 89, and 90, Table I) cardiac dilatation was present at the time infusion of blood was begun, and all of the dogs died before it was completed. Arterial pressure had been kept at  $\pm 40$  mm. Hg during the period of hypotension and was not excessively low when treatment was begun. The lowest was in Exp. 89 (Table I) in which the pressure was 28 mm. Hg. The average increase in the cardiometer record of diastolic volume was 11.6 mm. Intrathoracic venous pressure increased as cardiac dilatation occurred, the minimum being 0.6 cm. of water and the maximum 3.7.

Intravenous infusion caused an increase in stroke volume and a decrease in heart rate in all experiments. Cardiac output increased in three and decreased in two experiments. Arterial pressure did not rise in any of these experiments. Venous pressure increased moderately during infusion. Death occurred suddenly and was preceded by cessation of spontaneous respiration in all experiments. Artificial respiration failed to save the dogs.

#### TREATMENT OF POSTHEMORRHAGIC HYPOTENSION BY THE ADMINISTRATION OF A DRUG AND INFUSION OF BLOOD

*Tuamine.*—The preceding experiments demonstrated that circulation could not be restored by intravenous infusion of blood alone if withheld until sufficient cardiac dilatation occurred. Further, it is evident that tuamine sulfate, because of its stimulant action on the heart, might aid in restoration of the circulation, so averting the failure of blood alone. To demonstrate this, ten experiments were performed (Table II) in dogs with severe grades of cardiac dilatation. Tuamine was first injected and quickly followed by intravenous infusion of whole blood. Circulation was restored in all of these animals. The average increase in cardiac output was 30 per cent at the end of the infusion. The infusion produced a temporary rise in venous pressure and diastolic volume, but was less when tuamine was used prior to infusion, than in those treated by blood alone, despite the fact that the rate of administration averaged 40 c.c. per minute, while when blood alone had been given it was only 26 c.c. per minute. In five of the ten experiments in which the combined form of treatment was used, spontaneous breathing had ceased before tuamine was given.

The results of a typical experiment (No. 77) are illustrated in Fig. 2. At *T* (Section III) 20 mg. of tuamine were injected and the effects of the drug alone are shown in the remainder of this section. Section IV was

taken immediately after the infusion ended. The restoration of stroke volume and arterial pressure are illustrated. Likewise, the rise in venous pressure and diastolic volume produced by the infusion are apparent. Section V was taken fifteen minutes later, when cardiac output and arterial pressure were higher than the prehemorrhagic level. Venous pressure and cardiac size had returned to their control level.

Two experiments were performed in which fortuitously the conditions were exceptionally similar and hence serve to illustrate the effect of the combined treatment (Exp. 63 and 75, Fig. 3).

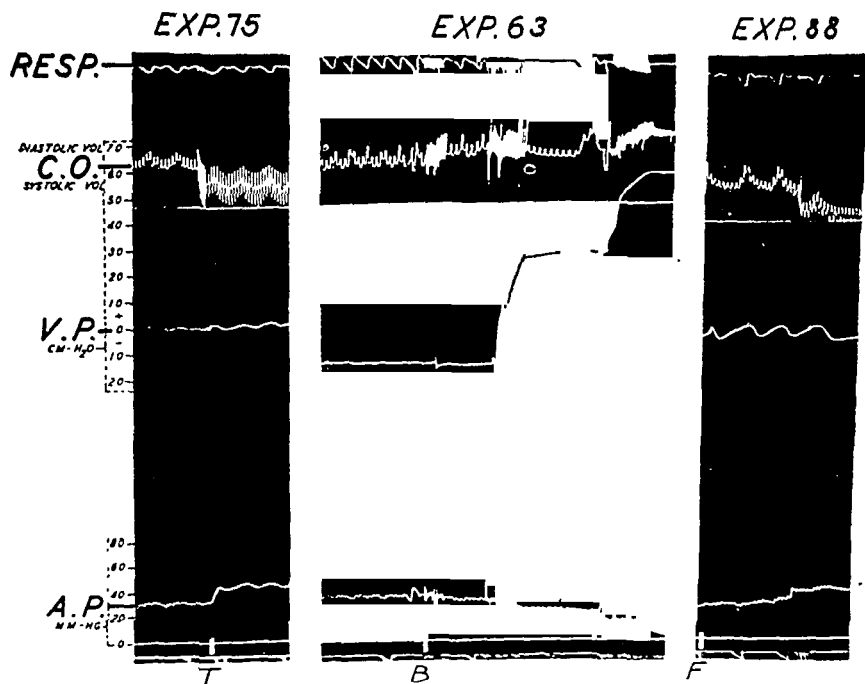


Fig. 3.—Treatment of posthemorrhagic hypotension by drugs and by infusion of blood alone. *Resp.*, Rate and depth of respiration; *CO*, cardiometer record; *VP*, venous pressure, and *AP*, arterial pressure.

*Exp. 75*, Circulatory effect of tuamine sulfate during phase of cardiac dilatation—*T* 20 mg. tuamine injected; *Exp. 63*, treatment of posthemorrhagic shock during cardiac dilatation by infusion of blood *B* (infusion began); *Exp. 88*, circulatory effect of fouramine during phase of cardiac dilatation; *F* (30 mg. 4-amine injected).

The effect of tuamine on the heart is apparent in *Exp. 75* (Fig. 3). Although cardiac output was doubled, the arterial pressure increased only 12 mm. Hg. In *Exp. 63* (Fig. 3) in which the status of circulation was similar to that of *Exp. 75*, the infusion of blood without tuamine had a disastrous effect. Cardiac output decreased from 0.5 to 0.14 liter per minute, arterial pressure declined, venous pressure rose, and the heart dilated. In another experiment the blood was given before the tuamine. The infusion was started when 1.8 stroke volume units of cardiac dilatation were present. After the infusion of 80 c.c. of blood, cardiac dilatation had increased to 2.6 units, and tuamine was admin-

TABLE XII  
CONDITIONS DURING HYPOTENSION AND BEFORE TREATMENT

	EXP. 63 DOG'S WEIGHT 11.2 KG.	EXP. 75 DOG'S WEIGHT 11.5 KG.
Systolic dilatation units	2.6	2.4
Blood removed per cent body weight	2.6	2.7
Time in min. required to produce requisite dilatation	105	64
Cardiac output at end of hypotensive period liter per min.	0.5	0.5
Arterial pressure mm. Hg	40	32
Treatment	No tuamine	30 mg. tuamine
Rate of blood infusion c.c. per min.	35	34

istered, but it was ineffective in preventing further cardiac dilatation and ultimate failure.

*Fouramine* (2-amino-4-methyl hexane sulfate).—Fouramine was administered in four experiments (Exp. 84, 86, 87, and 88, Table III) prior to the infusion. Treatment was not begun until systolic dilatation reached three or more stroke volume units. Thus, the severity of shock in these was equal to, and in some experiments exceeded, that present in the experiments in which tuamine had been used.

The effect of this compound on the circulation is illustrated in Exp. 88, Fig. 3. The changes in stroke volume and systolic volume are striking and are similar to those produced by tuamine. Cardiac output was increased from 0.27 to 0.84 liter per minute but arterial pressure rose only 12 mm. Hg. In three of the four experiments, fouramine and infusion restored circulation to its prehemorrhagic level. In Exp. 87 (Table III), in which five stroke volume units of cardiac dilatation were present, fouramine failed to reduce cardiac size and the dog died during the infusion.

*Oneamine* (1-amino heptane sulfate).—In two experiments (Nos. 97 and 98, Table III) in which oneamine was substituted for tuamine, the circulation was not restored by infusion of the blood which followed its administration. In Exp. 97 there appeared to be some temporary improvement after the drug was administered but it was of short duration. Within four minutes, arterial pressure had been elevated from 38 to 100 mm. Hg, and cardiac output increased from 0.6 to 1.8 liters. The latter was not maintained and seven minutes later it had decreased to 0.73 liter per minute, although the infusion continued throughout the period. Arterial pressure returned to 46 mm. Hg and the dose of oneamine was repeated. The second injection had no evident effect and the dog died with low blood pressure twelve minutes after infusion was complete.

Oneamine also failed to reduce cardiac size in Exp. 98 (Table III) and cardiac output was decreased rather than increased. The infusion was ineffective.



*Paredrine.*—One cubic centimeter of 1 per cent paredrine was administered just prior to infusion in two experiments (Exp. 94 and 96, Table III). The injection of paredrine was very effective in reducing heart size in one experiment (No. 94) in which cardiac dilatation was present to the extent of 3.4 stroke volume units. The systolic volume decreased 35 mm. and stroke volume and heart rate increased. Arterial pressure increased immediately from 34 to 90 mm. Hg and when the infusion was ended, the circulation had been restored. But in Exp. 96 (Table III), although the degree of shock was not excessive (1.6 stroke volume units), administration of paredrine did not change the cardiodynamic pattern during the two minutes of the dog's survival. The cardiac action was much slower in its onset than that of tuamine.

*Adrenalin.*—One dog (Exp. 91, Table III), (1.6 stroke volume units) was treated with 30 gamma of adrenalin just before infusion. During the three minutes the dog survived after it was given and while being infused, no change in cardiac output or arterial pressure occurred. The same dose of adrenalin when administered in the prehemorrhagic period to this dog increased cardiac output from 1.2 to 2.2 liters per minute and elevated arterial pressure 64 mm. Hg.

The loss of responsiveness to adrenalin during prolonged posthemorrhagic hypotension has been described by Rous and Wilson (1919) and by Page (1942). In Exp. 92 (Table III) a large dose (1,000 gamma) was administered when a severe degree of hemorrhagic shock was present (five stroke volume units). The adrenalin increased stroke volume from  $\pm 2$  to 8 c.c., heart rate from 100 to 180, and thus cardiac output from 0.2 to 1.4 liters per minute. Together with the infusion of blood, adrenalin raised arterial pressure from 28 to 100 mm. Hg. However, the effect was very brief and although the infusion was continued, cardiac output and arterial pressure began to decline after four and one-half minutes. When the infusion ended, cardiac output was 0.63 liter per minute and arterial pressure was 30 mm. Hg. Heart rate and respiration were slow and the dog died one minute later.

From these results it is apparent that the action of adrenalin is too fleeting to be of value in this method of treatment of severe post hemorrhagic shock.

*Changes in Roentgenograms of the Heart During Posthemorrhagic Hypotension and Its Treatment.*—In the preceding experiments, changes in cardiac size which occurred during hypotension and the period of treatment have been calculated from cardiometer records. As a more direct approach, photographs were taken of the chest with a portable x-ray machine at intervals during experiments in which the cardiodynamic changes were simultaneously being recorded by a cardiometer.

It was important that the position of the dog and the x-ray machine remain constant throughout the experiment; therefore, a special board was constructed which made it possible to slip a cassette under the dog's

back without moving the animal. This was accomplished by constructing a bridge of plywood 2 cm. above the surface of the dog board. Corks were nailed along the board to prevent any lateral motion of the animal.

In all experiments the changes in heart size as estimated from transverse cardiac diameter of the heart shadow were found to parallel those recorded by the cardiometer. These are shown in a typical experiment in Fig. 4. The reduction in size during bleeding and the first part of the hypotensive period were easily discernible, being 1.2 cm. maximum and 0.5 cm. minimum. As hypotension was continued, a progressive increase in cardiac shadow occurred and this appeared simultaneously with the increase in diastolic volume observed in the cardiometer records. Just before treatment was begun, the shadow was slightly larger than during the prehemorrhagic period and much larger than during the first part of the hypotensive period.

The increase in cardiac silhouette above the point of maximum reduction in size, that is, from point *B* (Fig. 1) during the terminal phase of hypotension, varied from +0.8 to +1.5 cm. But change in silhouette, as was to be expected, could not be correlated with stroke volume units. The largest increase did not occur in the experiment with the largest increase in stroke volume units.

Hypotension in these experiments was treated by the injection of fouramine or tuamine and infusion of blood. The cardiac shadow decreased after treatment was completed in four experiments in which circulation was restored, but in one in which treatment failed it continued to increase after the infusion ended.

*Tachyphylaxis.*—Administration of a single large dose (50 mg.) of oneamine caused the blood pressure to rise 100 mm. Hg or more. A second dose given after the arterial pressure had returned to its initial value elicited little or no rise and a third dose usually caused a fall. Tuamine and fouramine caused no rise and commonly a fall instead. Reversing the order of administration, it was possible to make dogs tachyphylactic by means of tuamine or fouramine to oneamine. Thus, cross tachyphylaxis is produced by a fairly broad group of structurally related amines. It seldom lasts more than an hour.

Pithing the dog, once tachyphylaxis has become established, does not, as is the case with adrenalin, enhance the pressor response.

The pressor action of angiotonin, a peptide, was not blocked by prior tachyphylaxis to these amines.

*Treatment of Posthemorrhagic Hypotension in "Intact" Dogs by Administration of Tuamine and Infusion of Blood.*—In the preceding experiments application of a cardiometer precluded observations on the survival of the dogs in which the circulation had been restored. Therefore, eight experiments were performed in which the occurrence of cardiac dilatation was determined by the radiographic method. Roentgenograms were taken before bleeding, at intervals during the hypotensive period, and after circulation had been restored by treatment.



Fig. 4.—X-ray photographs taken before and during prolonged posthemorrhagic hypotension. X-rays were taken during hypotensive period of Exp. 84 (Table III).  
 (1) Photograph of roentgenogram taken during prehemorrhagic period. (2) Photograph taken during hypotensive period when cardiometer indicated greatest reduction in cardiac size. (3) Photograph taken just before treatment began. Cardiometer indicated an increase of 3.5 stroke volume units in systolic volume.

Arterial pressure was reduced to 40 mm. Hg by intermittent bleeding. Hypotension was maintained at this level until evidence of increase in cardiac silhouette was observed on the x-ray photographs and then it was prolonged until death of the animal appeared imminent because of a sharp decline in arterial pressure or decrease in both rate and depth of respiration.

The cardiac silhouette progressively decreased in size during bleeding in the primary stage of hypotension. The maximum reduction in the transverse diameter of the cardiac shadow was 2.4 cm. and the minimum 1.0 cm. As hypotension was continued the decrease in the cardiac silhouette changed to an increase. The longest period of hypotension which elapsed prior to the appearance of an increase in cardiac shadow was 112 minutes, and the shortest, 60 minutes. In four experiments

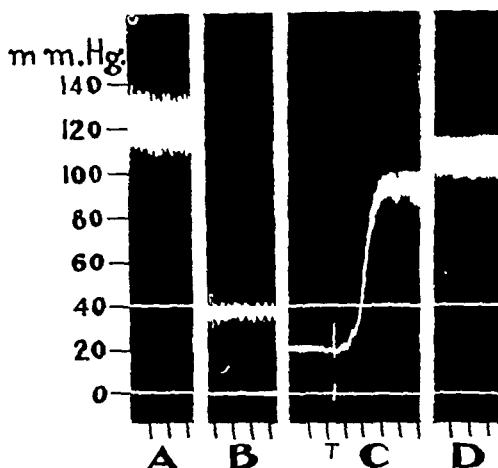


Fig. 5.—Treatment of posthemorrhagic shock by administration of tuamine sulfate, followed by intravenous infusion of blood. Dog's weight: 12.8 kg.

Section A, Prehemorrhagic period; Section B, after 122 minutes of sustained hypotension produced by removal of 520 c.c. of blood; Section C, after 193 minutes of sustained hypotension and radiographic evidence of cardiac dilatation, arterial pressure had declined to 20 mm. Hg, at T, 25 mg. tuamine were injected and began intravenous infusion at rate of 50 c.c. per minute; Section D, thirty minutes after infusion had been completed, arterial pressure remained within limits of normal.

an intra-arterial injection of 20 to 30 c.c. of blood was necessary to maintain the arterial pressure during the terminal portion of the hypotensive period. This injection of blood temporarily maintained the arterial pressure but did not halt the cardiac dilatation. The average duration of the hypotensive period after the onset of the phase of cardiac dilatation was forty-three minutes. The maximum increase in the transverse diameter over the minimum observed during hypotension of the cardiac silhouette was 0.8 cm., and the minimum, 0.4 cm.

When death appeared imminent, the animals were treated by injecting 2 mg. per kilogram of tuamine sulfate and this was immediately followed by a rapid infusion of blood intravenously. This treatment produced an immediate rise in arterial pressure (Fig. 5). The average

rate of intravenous infusion was 50 c.c. per minute and within three minutes in all experiments arterial pressure was more than 100 mm. Hg. In six dogs this elevation was permanent and the animals recovered. In two the rise was temporary and both dogs died within one hour after the infusion ended. The average arterial pressure at the end of the infusion in the six dogs which recovered was 134 mm. Hg and in these the average arterial pressure twenty-four hours later was 122 mm. Hg. At this time hematocrit and the plasma proteins were normal.

In all experiments the roentgenograms taken as the infusion ended showed an increase in the size of the cardiac silhouette. The heart shadow was now larger than it had been in the prehemorrhagic period. In the six dogs which recovered after infusion was completed and circulation stabilized, the cardiac silhouette gradually decreased so that in the pictures which were taken thirty to sixty minutes after infusion it was smaller than it had been in the prehemorrhagic period. In the two dogs in which treatment failed, the cardiac shadow in the roentgenograms taken after treatment did not decrease but continued to increase as arterial pressure declined.

#### DISCUSSION

One of the chief objections to the use of a cardiometer in the study of circulatory dynamics has been that conditions of the experiments were very abnormal since the normal pressure relations in the thorax were disturbed. This objection has been overcome in our experiments by closing the opening in the pleura and restoring negative pressure. The importance of this maneuver has been demonstrated by Boyd and Patras (1941). The fact that the venous arterial pressures and circulation time were the same after the cardiometer was applied as before is evidence that it did not interfere with cardiac function.

The changes in circulatory dynamics during posthemorrhagic shock obtained under conditions of these experiments were similar to those observed by Abell and Page (1942) in the blood vessels of cats' mesenteries and rabbits' ears. They found by direct microscopic observation that the arterioles and arteries were constricted by active muscular contraction after severe hemorrhage and that relaxation of these vessels occurred in the terminal stages of shock. The reduction in cardiac size during the first phase of hypotension is comparable to the stage of vasoconstriction, while dilatation of the heart is associated with the stage of relaxation of the arterioles. This similarity of behavior of peripheral vessels and the heart is to be expected if we remember that the heart is only a specialized portion of the vascular system.

The progressive nature of the changes in circulatory dynamics which occur as posthemorrhagic hypotension is continued have been demonstrated. During the period of bleeding, there was a rapid decline in stroke volume and cardiac output, but the change in pulse rate was variable. The need to modify the concept that pulse rate varies in-

versely with fall in blood pressure and cardiac output has already been pointed out in clinical studies by McMichael (1944). After arterial pressure had been fixed at a hypotensive level and no more blood was withdrawn, cardiac output and heart size continued to decrease as hypotension was further prolonged. Definite changes appeared in the cardiodynamic pattern. Diastolic and systolic volume began to *increase* rather than decrease. Stroke volume continued to decrease and the heart rate grew slower. These changes resulted in a further decline in the already reduced cardiac output. Venous pressure rose concurrently with the rise in heart size, but arterial pressure remained constant for some time after the onset of dilatation, to be followed by a decline and death. Arterial pressure could be maintained for a long time by intermittent intra-arterial injections of 35 to 50 c.c. portions of blood, but this did not decrease the rate of cardiac dilatation.

The rate at which cardiac dilatation occurred in the terminal phase of shock varied considerably. In those animals in which it occurred rapidly a greater degree of dilatation was tolerated than when the rate was slower. In five dogs in which respiration ceased before treatment started, the time between the onset of cardiac dilatation and cessation of respiration varied from seven to forty-four minutes. The demonstration by roentgenographic study of an increase in traverse cardiac diameter with an increase in cardiac size, as indicated by the cardiometer, is evidence that the cardiac volume changes recorded were not artifacts.

The changes in circulation time occurring in the early stages of post-hemorrhagic shock indicate that vasoconstriction and reduction in size of the heart are beneficial adaptations, for circulation time is shortened after having been prolonged by bleeding. As hypotension continues and cardiac dilatation occurs, it again lengthens.

We wished to produce a degree of posthemorrhagic shock which could not be satisfactorily treated by the infusion of blood alone, and therefore, it was essential that a satisfactory criterion be established for this degree of shock before undertaking a study of therapy. Many experiments were carried out in which various criteria such as the duration of hypotension, amount of blood removed, and the level of arterial pressure were used, but they all proved to be inadequate for our purpose. Even loss of responsiveness to adrenalin or reduction of stroke volume proved unsatisfactory because some dogs could be successfully treated by the infusion of blood alone when the requirements of these criteria had been fulfilled.

We observed that if hypotension had been continued until cardiac dilatation appeared, then treatment by blood alone failed. Five control experiments were carried out in which hypotension was continued until the stage of cardiac dilatation was present and then the infusion of blood started. Treatment by this method failed in all five experi-

ments. Administration of blood seemed to hasten cardiac failure rather than overcome it. If the rate of infusion was reduced sufficiently so that cardiac dilatation did not increase, then it was so slow that the animal died before it could be completed. Having shown that shock of great severity could be produced and also the intensity of it measured to a degree, we attempted to augment the treatment by blood infusion with drugs.

From our observations of the circulatory changes produced by prolonged posthemorrhagic hypotension, it seemed probable that the most important action of such a drug would be to augment the output and force of the heart. If the cardiodynamic pattern could be changed from one of progressive dilatation to constriction and increased output, then infusion of the blood would not have the deleterious action that it does. Of the drugs studied in normal and hypotensive animals, tuamine, paredrine, and adrenalin produced the desired change. Of these, tuamine appeared the most satisfactory because not only did it increase stroke volume but it decreased the diastolic volume. Since, in comparison with adrenalin and paredrine, it caused a proportionately greater increase in cardiac output than in arterial pressure, it seemed less active as a peripheral vasoconstrictor. Wiggers and Middleton (1944) have demonstrated that peripheral resistance increases as cardiac output declines in early hemorrhagic shock, and therefore, if a drug increases peripheral resistance at this time, it would be harmful rather than beneficial. In the late stage of shock, when the heart fails and arterioles are partially dilated, still the imposition of vasoconstriction will intensify rather than lessen the basic defect, the insufficiency of tissue perfusion. Such insufficiency of perfusion, with resultant anoxia and metabolic change, determines the character of shock and, while the larger emphasis of this report is laid on the participation of the heart in causing it, we do not overlook the significance of concurrent changes in other parts of the vascular system, nor in other systems than the circulatory.

Recently we have had an opportunity to observe the effect of increased cardiac output and low arterial pressure in a patient in whom this condition had been brought about by a large dose of arsenic trioxide (Page, Taylor, Kohlstaedt, 1943). In this patient cardiac output was 5.3 liters and arterial pressure by direct measurement 30 mm. Hg, which resulted in a calculated peripheral resistance of 17 (normal 100). The patient was cooperative, able to move about at will, and suffered no deleterious effect from the hypotension, except urinary suppression. This observation emphasized to us that better tissue perfusion is desirable in the treatment of shock rather than elevation of arterial pressure. Tuamine appeared to be a substance which caused improvement in cardiac output with the least rise in arterial pressure and the smallest change in peripheral resistance.

We did not expect tuamine alone to restore circulation to its pre-hemorrhagic level, but only to produce sufficient improvement so that intravenous infusion of blood would be effective and possible once cardiac dilatation had occurred. This proved to be true. Stroke volume and cardiac output were restored in all the dogs by the combined method of treatment, whereas when treated by blood alone, stroke volume increased in some dogs temporarily but cardiac output was not increased. The heart rate decreased rapidly in those experiments in which stroke volume was increased. The rate of rise in arterial pressure in the dogs which received tuamine and blood closely simulated that produced by intra-arterial infusion in less severely shocked animals (Kohlstaedt and Page, 1943).

Oneamine was not as effective as tuamine because its action was of shorter duration. Fouramine seemed about as effective as tuamine. Paredrine had somewhat similar circulatory dynamic action, but it was considered less suitable because of the slow onset of its action and because it did not stimulate respiration to the same extent as tuamine. Adrenalin was of little value because of its very short action; a small dose was ineffective and a large dose produced a sharp increase in peripheral resistance and proportionately less increase in cardiac output. Therefore, it might even be harmful because of further increase in peripheral resistance without concomitant increase in cardiac output.

Oneamine, tuamine, and fouramine all produced crossed tachyphylaxis, usually after the second large dose, a tachyphylaxis apparently limited to amines of similar structure because angiotonin, a peptide, was unaffected in its pressor response in the face of established amine tachyphylaxis. The refractory period lasts about one hour in dogs. Unlike adrenalin, pithing does not enhance the response to these amines.

Having shown that circulation could be satisfactorily restored with the cardiometer in place, it seemed desirable to perform experiments in which survival could be studied and yet use a criterion of the severity of shock similar to the one established using the cardiometer. Measuring the transverse cardiac diameter by means of the x-ray proved quite satisfactory. Six of eight dogs treated by the combined method made complete recoveries after having reached the stage of cardiac dilatation.

In these experiments a longer period of hypotension elapsed in every instance before cardiac dilatation was detected by the radiographic method than had elapsed before it was shown by the cardiometer. This is due to the fact that the cardiometer is able to detect smaller changes in cardiac size, and possibly also that the application of the cardiometer added to the severity of the shock. An effort was made in these eight experiments to prolong hypotension as long as possible to achieve the greatest amount of cardiac dilatation before treatment was instituted. The very rapid rise in arterial pressure produced by the combined method of treatment was comparable to that observed in the dogs in which less severe posthemorrhagic shock had been treated by intra-



arterial infusion of blood (Kohlstaedt and Page, 1943). Definite improvement in depth and rate of respirations was produced by tuamine in these dogs.

A matter of importance in terminal hemorrhagic shock is the rate at which blood is infused. If it is too rapid, further dilatation of the heart occurs and death is hastened. If, on the other hand, it is too slow the progressive failure of the circulation continues almost unchecked and the animal succumbs before an adequate amount of blood is made available. It was a striking observation, therefore, that when the infusion of blood was preceded by the administration of tuamine, much greater rates of infusion were tolerated than without the drug. The rate was almost comparable to that when the intra-arterial method of infusion is employed, a very rapid rate indeed in some cases.

#### SUMMARY

1. Studies on the circulation of anesthetized dogs were made before and after prolonged hemorrhagic hypotension by records of stroke volume and cardiac size with the closed chest type of cardiometer (Boyd) of intrathoracic venous pressure, circulation time (NaCN method), arterial pressure, and respiration. The effects of methyl iso-thiourea, angiotonin, paredrine, neosynephrin, adrenalin, mixtures of ephedrin and pitressin, and the amines, oncamine (1-amino heptane sulfate), tuamine (2-amino heptane sulfate), and fouramine (2-amino-4-methyl hexane sulfate), were observed before and after hemorrhage in a search for a substance which would aid in restoring the circulation once it had seriously failed. Other experiments were carried out in which the cardiometer was not used, but the changes in heart size were estimated from x-ray photographs, so allowing survival of the animals to be studied.

2. Hemorrhage caused immediate reduction in stroke volume, diastolic volume, and venous and arterial pressure, followed by a rise in venous and arterial pressure, but maintenance of the reduced stroke volume and diastolic volume. After a prolonged period of hypotension, venous pressure rose sharply and this was followed by progressive increase in heart size despite further bleeding. Since systolic volume increased more rapidly than diastolic, stroke volume grew smaller as dilatation progressed and cardiac output was further decreased by bradycardia. In this terminal period when the size of the heart was increasing, administration of plasma usually precipitated circulatory collapse and death.

3. Methods for the recognition of the terminal ("irreversible") phase of shock were studied and all found wanting except for one. This was the determination of the relative amount of cardiac dilatation. A "stroke volume" unit was ascertained by measuring the height of the cardiometer tracing at that point when cardiac dilatation could first be

detected. When the systolic volume had risen to a point equal to the height of the stroke volume, one unit of dilatation had occurred; almost no animals survived despite attempts to reinfuse blood.

4. Among the various drugs tested on both normotensive and hypotensive animals, tuamine was selected chiefly because of its quick stimulating action on the heart without significant peripheral vasoconstrictor action.

5. Tuamine, like oneamine and fouramine, causes crossed tachyphylaxis limited to structurally related amines but not extending to peptides such as angiotonin. These amines differ from adrenalin in that destruction of the nervous system does not enhance their pressor action.

6. Injection of tuamine immediately followed by infusion of blood allowed the blood to be given at a fast rate. The combined treatment caused a sharp rise in arterial pressure, usually to normal, which in most cases was sustained.

Experiments in which survival was sought were performed without the use of the cardiometer but by determining cardiac dilatation by means of x-ray photographs. Most of these animals recovered when given the combined treatment despite the very severe conditions imposed.

We wish to express our grateful appreciation to Mr. Clifford Wilson for his assistance.

#### REFERENCES

1. McMichael, J.: *J. A. M. A.* 124: 275, 1944.
2. Kohlstaedt, K. G., and Page, I. H.: *Arch. Surg.* 47: 178, 1943.
3. Wiggers, C. J., and Werle, J. M.: *Am. J. Physiol.* 136: 421, 1942.
4. Page, I. H.: *Am. J. Physiol.* (In press.)
5. Boyd, T. E., and Patras, M. C.: *Am. J. Physiol.* 134: 74, 1941.
6. McGeorge, M., Sherif, M., and Smirk, F. H.: *J. Physiol.* 100: 474, 1942.
7. Bourne, W.: *Surg., Gynec. & Obst.* 68: 519, 1939.
8. Rous, P., and Wilson, G. W.: *J. Exper. Med.* 29: 173, 1919.
9. Page, I. H.: *J. Exper. Med.* 78: 41, 1943.
10. Page, I. H., and Abell, R. G.: *J. Exper. Med.* 77: 215, 1943.
11. Wiggers, H. C., and Middleton, S.: *Am. J. Physiol.* 140: 677, 1944.
12. Page, I. H., Taylor, R. D., and Kohlstaedt, K. G.: *Am. J. Med. Sci.* 205: 730, 1943.
13. Melville, K. I.: *J. Pharmacol. & Exper. Therap.* 44: 279, 1932.

# Review of Recent Meetings

## MEETING OF THE AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS AT STOCKBRIDGE, MASS.

JUNE 8 TO 10, 1944

C. D. CREEVY, M.D., MINNEAPOLIS, MINN.

*Wednesday, June 8*

A CASE reported by M. F. Campbell, New York, described a varicocele in a boy of 12 years. It proved to be due to compression of the spermatic vein by aberrant renal vessels. Cure followed division of the aberrant vessels and of the spermatic vein.

His second case report concerned a premature infant with retention of urine apparently due to a birth injury to the nervous system. Recovery followed prolonged use of an inlying catheter.

Charles M. McKenna of Chicago described two cases of true lateral hermaphroditism with hypospadias. In each instance what was thought to be an undescended left testis proved to be an ovary. The presence of a testicle on the right side was proved by biopsy. They were treated by left oophorectomy, straightening of the penis, and urethroplasty.

C. M. Davis, Philadelphia, has evolved rather a complicated method of treating midscrotal hypospadias. Because of the location of the external urinary meatus it is, in his opinion, impractical to divert the urine during healing of the urethroplasty, by means of the usual perineal urethrostomy. After preliminary straightening of the penis, he constructs the glandular urethra from the foreskin, and the penile urethra by the method of Duplay. However, the Duplay plastic is continued behind the external meatus to the posterior edge of the scrotum, and a catheter is inserted through this accessory canal into the bladder. When healing is complete, the accessory canal is excised.

C. L. Deming, New Haven, treated a patient for papillomatosis of the urethra and carcinoma of the bladder by repeated fulguration of the urethra, excision of the carcinoma of the bladder, and finally by removal of the penile urethra because of recurrence. Twelve years after the first treatment, one lung was removed because of metastases. One year later, however, there was evidence of metastasis in the ilium.

H. J. Jewett, Baltimore, has done twenty-five ureteroenterostomies and total cystectomies for carcinoma of the bladder. Having observed that a stony induration of the outer surface of the bladder ordinarily meant early recurrence and death, he reviewed the protocols of 107 autopsies in vesical carcinoma, and found no metastases when the growth was confined to the mucosa and submucosa, a few when there was but little invasion of the muscularis, and many (52 of 89) when the outer coats of the bladder were invaded. Bimanual palpation of the bladder under anesthesia is of great value in detecting the penetration of the wall of the bladder which means that cure by any method is very unlikely.

A. J. Scholl of Los Angeles had a patient with a vesical diverticulum containing a papillary carcinoma as well as an xanthoma which extended out of the

diverticulum onto the adjoining vesical mucosa. The patient was well one year after excision of the lesions. Scholl cited the occurrence of the xanthoma in the bladder as a curiosity.

**R. C. Graves** of Boston has done ureteroenterostomy and total cystectomy for vesical carcinoma a number of times since 1933. He transplants one ureter at the first stage, and at the second transplants the other ureter and removes the bladder. He employs continuous spinal anesthesia with great satisfaction. One patient is well 10½ years after operation and has a normal excretory urogram.

In the discussion **G. G. Smith**, Boston, reported ten cystectomies in the past year with but one death. **Quinby** of Boston and **Colby** emphasized their view that external irradiation should not be employed in any tumor of the bladder which is amenable to operation.

**F. H. Colby** of Boston discussed an unusual syndrome called Reiter's disease, characterized by conjunctivitis, polyarthrititis, prostatitis, and urethritis. In his three cases, smears and cultures of discharge from the eyes, joint fluid, urethral discharge, prostatic secretion, and urine were negative, and chemotherapy, including penicillin, was of no avail. The cause of the disease is unknown. All patients recovered.

**G. R. Livermore**, Memphis, treats urethral strictures by means of a bougie carrying a laterally placed strip of copper. Under local anesthesia, current from a surgical diathermy machine is passed through a strictured area. The current used is not strong enough to cut but is intended to cause shrinkage of the tissue. Periodic dilatations are continued. Livermore believes that the method facilitates dilatation and delays recontraction. It may be used more than once in a given case.

**J. A. Taylor**, New York, had a patient who had had excisions of epithelial horns of the glans penis on five different occasions. He has been free of recurrence for a year or so, but Taylor anticipates more recurrences.

In the discussion, **Huggins** called attention to the similarity between this lesion and the papillomas of the penis occurring in a certain strain of wild rabbit. The lesion in the rabbit is transmissible, and is thought to be due to a filtrable virus.

#### *Friday, June 9*

**G. S. Foulds**, Toronto, described a case of renal calculus due to an adenoma of the parathyroid, which was removed.

**H. G. Hamer** and **H. O. Mertz** of Indianapolis were able to dissolve a recurrent renal calculus (two previous operations) composed of alkaline earths by prolonged irrigation with the "solution G" of Suby and Allbright.

**H. G. Bugbee** of New York, who was awarded the Keyes medal for achievement in urology, described a technique for nephrolithotomy for branched renal stones in which Gerota's (perirenal) fascia is left attached to the kidney. This fibrous layer, thickened by the previous operation, serves to hold the mattress sutures with which the nephrotomy is closed around a nephrostomy tube.

**H. C. Bumpus** of Pasadena did a left nephroureterectomy for a pyonephrosis due to ureteral calculi in a hypoplastic kidney in a 27-year-old male with severe hypertension. The systolic pressure dropped from 220 to 150, but a few days later paroxysmal dyspnea and hypertension appeared, and the patient died on the fourteenth postoperative day in uremia. At autopsy the artery to the remaining kidney contained a thrombus. The essayist believed that the sequence of events indicated that the hypertension was renal in origin, coming originally from the left kidney and, when thrombosis and infarction developed after the left nephrectomy, from the right.

**W. F. Braasch**, Rochester, Minn., reviewed the various unilateral renal lesions which may cause hypertension. He was unable, in a study of a large series of

patients with nephroptosis, to uncover evidence indicating any relationship between renal ptosis and hypertension.

In the discussion of the papers, **Barney and Colby of Boston and Keyser of Roanoke** pointed out that many stones have organic matrices or nuclei which are insoluble in solution G, and that very compact calculi are themselves insoluble. Keyser suggested that a  $\frac{1}{2}$  per cent solution of urease might effect a dissolution of the organic material in some cases. **Colston (Baltimore)** dissolved a recurrent calculus by long-continued irrigations with solution G through a nephrostomy.

**Scholl**, also in the discussion, reported several cases of hypertension in which bilateral narrowing of the aortic orifices of the renal artery was found at necropsy. **Nesbit, Ann Arbor**, had no success with nephrectomy for hypertension in renal hypoplasia.

**J. C. McClelland, Toronto**, succeeded in excising a papillary carcinoma of the pelvic ureter and making an end-to-end anastomosis. It was done quite recently.

**A. I. Dodson of Richmond, Va.**, described what he thought to be a large diverticulum, containing a stone, in the pelvic ureter of a woman. It was treated by local excision and nephrectomy. Since there was a duplication of the left renal pelvis, the reviewer ventures to suggest that this was an instance of an ectopic ureteral orifice ending in a cyst of Gaertner's duct.

**V. J. Oconor, Chicago**, presented a case in which pain in the left flank had been present for fifty years. The patient proved to have a diverticulum of the right wall of the bladder, a large stone in the left ureter, a left hydronephrosis containing 4,800 c.c. of urine, and a benign hypertrophy of the prostate. Treatment, which was successful, included vesical diverticulectomy, cystostomy, ureterolithotomy and ureterostomy (one stage), transurethral resection, and nephroureterectomy.

**J. D. Barney, Boston**, gave a follow-up report upon a patient who had a nephrectomy for adenocarcinoma in 1932, and a pulmonary lobectomy for metastases in 1933, and who was living and well in 1944. Such solitary metastases are exceedingly rare.

**N. J. Heckel of Chicago** excised a mass from the spermatic cord and found it to be a tuberculoma. He could find only two cases in the literature. In the discussion **Barney** reported a similar case, the patient well twenty-five years after excision of the mass and corresponding testicle.

**B. S. Barringer, New York**, reviewed a considerable series of testicular neoplasms. Eighty per cent were classified as seminomas, and 17 per cent as adenocarcinomas. They were treated by orchidectomy and external irradiation. Thirty per cent of the patients were well five years after treatment, including several who had abdominal metastases when treatment was started.

**W. H. Toulson, Baltimore**, treated a young negro man with elephantiasis of the penis and scrotum due to lymphogranuloma, by simple excision and skin grafting with a good end result.

*Saturday, June 10*

**Charles Huggins of Chicago** discussed an enzyme found in the normal prostatic secretion and capable of liquefying clotted blood or semen. It is a globulin, and is present in increased amounts in long-standing prostatitis.

**N. P. Rathbun of Brooklyn** reviewed the results of castration in twenty-three cases of carcinoma of the prostate done in the last three years. Only two were not benefited. There was, however, nothing resembling a cure.

**R. M. Nesbit, Ann Arbor**, compared the results which followed treatment of carcinoma of the prostate by castration (seventy-five cases) with those which resulted from the administration of estrogens, usually 1 mg. of stilbestrol daily (fifty cases). The two methods were about equally effective in relieving pain and in

increasing body weight. Castration was superior to therapy with estrogens in producing amelioration of obstruction to urination, shrinkage of the primary lesion, and regression of metastases. He called attention to a case in which an elevated serum acid phosphatase fell to normal after treatment and remained so until death although, at autopsy, the primary and metastatic lesions contained an abundance of acid phosphatase (special stains).

In the discussion, **Herbst** of Washington stated that some of his patients had developed avitaminosis while taking estrogens. He believed that the administration of thiamine and nicotinic acid had increased comfort and prolonged life in some of them. He advocates increased doses of estrogens when smaller ones fail, and castration if the larger ones are ineffective.

**Davis** of Philadelphia cited two cases of mania following the administration of estrogens.

**Dean**, New York, disagreed with **Nesbit**, stating that the reduction in the size of the primary tumor was greater with estrogens than with castration. Sixty per cent of his patients had relapses six to eight months after castration; he felt that those treated with stilbestrol remained comfortable longer, and that the greatest relief was seen in those patients with striking hypertrophy of the breasts.

**Huggins**, Chicago, has some patients who are clinically well four years and nine months after castration; bony metastases have disappeared completely on x-ray in five of eighty castrated patients. In his experience a failure after castration is not amenable to therapy with the estrogens, and vice versa. **Nesbit** disagreed with this view.

**A. L. Dean** of New York described the case of a young woman who had received heavy irradiation of the left abdominal area for what was clinically a lymphosarcoma. The mass disappeared, but 7½ years later she had a hypertension of 180/100. She proved to have a contracted left kidney with reduced excretion of diodrast and mannitol, but a normal differential phthalein. The left kidney was removed, and showed shrinkage of the lower half with advanced arteriosclerosis. The blood pressure has remained normal during the ensuing fourteen months.

**E. G. Crabtree** of Boston discussed a patient who had a leiomyoma of the kidney containing a hemorrhagic cyst, and who was well many years later.

**A. R. Stevens**, New York, described two cases in which polycystic kidneys were recognized years before death, and in which repeated cortical infections were relieved periodically by surgical procedures and by urinary antiseptics, but which finally caused death.

**Robin Pearse**, Toronto, discussed the acid-base equilibrium in urological patients, particularly those with prostatism. He emphasized the importance of discovering and correcting acidosis, usually by the administration of 5 per cent sodium bicarbonate intravenously.

**Emerson Smith**, Montreal, had several patients with essential hematuria, in whom the prothrombin time was prolonged, and whose bleeding ceased after the administration of vitamin K. He also advocated the use of dicumarol in hematuria with repeated urinary retention from clots when the causative lesion was inoperable, as in far advanced renal and vesical neoplasms, simply to prevent clotting in the bladder and to increase comfort. He had done this successfully in three cases.

**Leon Herman** and **L. B. Greene** of Philadelphia discussed diverticula of the female urethra and reported six cases. Simple excision is usually curative.

# THE TWENTY-SIXTH ANNUAL MEETING OF THE AMERICAN BRONCHO-ESOPHAGOLOGICAL ASSOCIATION

PAUL H. HOLINGER, M.D., CHICAGO, ILL.

THE twenty-sixth annual meeting of the American Broncho-esophagological Association was held June 6, 1944, in New York. The following papers were presented:

Robert L. Moorhead, Brooklyn, N. Y., presided. In his presidential address Moorhead mentioned the advances in the field of bronchology and esophagology which had taken place during the years in which the Association had held its meetings. He also discussed the future of bronchoscopy, stressing the role which chemotherapy applied bronchoscopically will play. Finally, Moorhead mentioned the limitations of bronchoscopy as a diagnostic aid. One example is the inability to obtain more than 75 to 80 per cent positive biopsies in suspected bronchogenic carcinoma. He suggested one means of improving this figure through the use of bronchoscopically directed needle biopsy.

Gabriel Tucker and Joseph P. Atkins (by invitation), Philadelphia, Pa.: **Recent Trends in the Bronchologic Use of Chemotherapeutic and Biotherapeutic Agents.**—These authors summarize their experience with the endobronchial and systemic administration of chemo- and biotherapeutic agents which may be applicable to various bronchopulmonary diseases. Autogenous vaccines were found to be useful adjuncts to the treatment of chronic tracheobronchitis and allergic tracheobronchitis. Epinephrine, administered ten minutes before bronchoscopy, was considered of value as an aid to bronchoscopic aspiration of secretions from asthmatic patients. They state that of the many drugs which have been applied locally in the bronchi for the treatment of infection, the sulfonamides and penicillin are the first which are both noninjurious to the lung and possess therapeutic effectiveness. The sulfonamides are introduced into the bronchi with a powder blower, macrocrystalline sulfanilamide and microcrystalline sulfathiazole being used. Penicillin used locally in the tracheobronchial tree was introduced in aqueous solution.

Porter P. Vinson, Richmond, Va.: **Treatment of Chronic Nontuberculous Pulmonary Infection by Bronchoscopy and Insufflation of Sulfonamide Compounds.**—Vinson states that since 1938 he has treated approximately 100 patients with chronic suppurative pulmonary disease other than abscess, by bronchoscopic aspiration followed by the intrabronchial insufflation of powdered sulfonamide preparations. He uses a mixture of two parts of sulfanilamide and one part of sulfathiazole. He stated that one-half of the patients thus treated had been benefited. No untoward results were observed in any of the patients. Improvement varied from almost complete relief of symptoms in patients with chronic asthmatic bronchitis associated with purulent secretion, to about 75 per cent reduction in cough and expectoration in patients with well-established bronchiectasis.

The papers of Tucker and Atkins, and Vinson were discussed together since their contents dealt with the same subject. William Lell, Philadelphia, demonstrated the manner in which the blood levels of the sulfonamide compounds varied with bronchial insufflation. Louis Clerf, Philadelphia, pointed out the fact that in the presence of pus the bacteriostatic action of the sulfonamide compounds is inhibited. Thus, the efficacy of their introduction into the purulent bronchiectatic areas was open to certain theoretical questions.

Received for publication, July 10, 1944.

## CASE REPORTS

**James A. Downing, Des Moines, Iowa: Unsuspected Safety Pin Penetrating the Posterior Mediastinum.**—Two case reports of safety pins perforating the esophagus and lodging in the posterior mediastinum were presented. In neither case could the history of the time of ingestion of the foreign body be obtained. The first infant, 18 months of age, had been seen by a physician because of difficulty in breathing. A bilateral pneumothorax was found with the safety pin in the posterior mediastinum. Chest aspiration and supportive measures were unsuccessful and the child died thirty-six hours following admission to the hospital. The second infant, 10 months of age, was also seen by a physician because of difficulty in breathing. X-ray pictures revealed a perforation of the esophagus and trachea by an open safety pin. The infant recovered following removal of the foreign body. These cases were presented because in neither case was the history of foreign body elicited, the parents consulting the physician because of respiratory difficulty.

**W. Likely Simpson, Memphis, Tenn.: Mediastinal Complications Associated With Esophagoscopy.**—Two cases of mediastinal abscess were presented. In the first case an esophagoscopy was followed by a mediastinal abscess in a patient with a carcinoma of the esophagus. In the second case mediastinitis followed an esophagoscopy which was done to remove a chicken bone. A mediastinotomy was performed for drainage of the posterior mediastinum and the patient eventually recovered.

**Clyde A. Heatly, Rochester, N. Y.: Perforation of the Lower Esophagus: Recovery With Chemotherapy and Gastrostomy.**—In this case mediastinal and subcutaneous emphysema with pleural and pneumonic changes at both lung bases followed an apparently uneventful esophagoscopy under general anesthesia. The procedure was performed for dilatation of a mild cardiospasm by means of a pneumatic bougie. This patient recovered. Treatment consisted of withholding all fluids and food by mouth, establishment and maintenance of a blood level of sulfadiazine of about 22 mg. per cent six days with subsequent gradual reduction and withdrawal on the twelfth postoperative day, and a gastrostomy which was continued for about three weeks. In conjunction with the mediastinal and subcutaneous emphysema, the patient developed a white blood cell count of 48,000 twenty-four hours following the perforation.

**William A. Lell, Philadelphia, Pa.: Safety Pin in the Esophagus With Perforation of the Pericardium.**—Lell presented a case of a 10-month-old infant suspected of having pneumonia, who was found on x-ray examination to have a safety pin in the lower esophagus. The cardiac shadow was markedly enlarged. Following removal of the safety pin, 30 c.c., and subsequently 15 c.c. more of purulent material were aspirated from the pericardium. Chemotherapy and transfusions were used. After a stormy convalescence the child made a complete recovery.

**Thomas Carmody, Denver, Colo.: Removal of Denture From Upper End of Esophagus.**—A large denture with several clasps impacted in the upper esophagus was extracted.

**John H. Foster, Houston, Texas: Impacted Foreign Body in the Esophagus Requiring External Removal.**—A 5-year-old boy who had swallowed a marble developed extreme difficulty in breathing. His mother attempted to remove the foreign body digitally, and this resulted in forcing the foreign body further down into the esophagus, from which attempts to remove it either upward or downward esophagoscopically were unsuccessful. An esophagotomy was necessary to extract



the impacted foreign body. In the discussion **Thomas Carmody**, Denver, described a similar case in which a radish became impacted in the esophagus causing a rupture of the esophagus. **James E. Cassidy**, South Bend, Ind., described a case of a marble in the esophagus with removal by a wire snare.

**H. L. Kearney**, New Orleans, La.: **Fatal Hemorrhage From Perforation of Right Renal Artery by Fish Bone.**—This patient, a man 45 years of age, swallowed a fish bone twenty-four hours prior to being admitted to the hospital. He complained of intense pain between the shoulder blades and had symptoms suggestive of a mediastinitis. The esophagoscopy examination was negative. The pain subsided after the esophagoscopy. Two months later he was readmitted to the hospital because of pain in the back and the abdomen and he was found to be acutely ill. A laparotomy demonstrated a large retroperitoneal hemorrhage and at autopsy a small needlelike fish bone was found in a perforation of the right renal artery. No perforation of the esophagus or of the remainder of the gastrointestinal tract was found to indicate the path of the foreign body but it was felt probable that perforation took place in the duodenum close to the right renal artery.

**Herman J. Moersch** and **Stuart W. Harrington** (by invitation), Rochester, Minn.: **Benign Tumor of the Esophagus.**—**Moersch and Harrington** present fifteen cases of benign tumors of the esophagus. These tumors are comparatively rare and are characterized by the fact that they usually reach considerable size before producing symptoms. In over 7,000 post-mortem examinations forty-four benign tumors of the esophagus were found and in none of these cases was there a history of esophageal difficulty. They divide the benign tumors of the esophagus into two types: those arising from the mucosa or submucosa, often called intramural, and those arising from the outer coats of the esophagus, or extramucosal tumors. The former are usually more apt to give symptoms of dysphagia than the latter. They are found more frequently in men than in women and may be encountered at any age, although they are most frequently found after the fourth decade. In the fifteen cases reported, the principal symptom was dysphagia and in several instances the history of regurgitation of the fleshy mass was obtained. Diagnosis is not easy and cannot always be established correctly by roentgen examination, since in the case of large tumors the lesion is frequently confused with that of cardiospasm. An esophagoscopy examination made for diagnosis is likewise not infallible. The error is attributable to the fact that the mucous membrane covering most benign tumors of the esophagus has the same appearance as the esophageal mucosa itself and is so interpreted. In their experience the leiomyoma is the most common type of benign tumor of the esophagus; lipoma, polyp, adenoma, hemangioma, fibroma, and fibrolipoma are the other types of tumors encountered. Treatment was dependent upon the size of the tumor and its location. Tumors with a long pedicle attached to the esophageal introitus were removed with a snare endoscopically. Large tumors were removed by esophagotomy, while small tumors producing few symptoms were considered not to require treatment.

**John D. Kernan**, New York, N. Y.: **Obstruction of the Right Main Bronchus Due to Congenital Maldevelopment of the Pulmonary Veins in a 4-Month-Old Baby.**—This infant had had attacks of cyanosis from birth, which increased in severity until continuous oxygen was necessary. Physical examination demonstrated a cardiac murmur over the entire chest and chest x-rays showed a widened superior mediastinum. Bronchoscopic examination demonstrated compression of the right main bronchus. On post-mortem examination a greatly dilated right superior vena cava was found, with a persisting left superior vena cava which produced compression of the right main bronchus. There were other extensive cardiovascular anomalies.

**Samuel Iglauer, Cincinnati, Ohio: Spontaneous Mediastinal Emphysema.**—In the case reported, a 3-year-old child suddenly developed crepitant swelling in the neck which soon extended over the face, trunk, and arms. There was no history of illness preceding the onset of the swelling except that of a slight cold. A bronchoscopic examination was done to rule out the presence of a foreign body and none was found. Because of increasing dyspnea, a midline incision was made in the neck through the pretracheal fascia to relieve the mediastinal tension. The child was placed in oxygen and sulfonamide therapy was instituted. Improvement was gradual at first but recovery was complete by the twelfth postoperative day. Iglauer believes that the pathogenesis of this mediastinal emphysema was directly from the alveoli along the sheathes of the pulmonic vessels and into the mediastinum, and that not infrequently this results in pneumothorax.

**Arthur E. Hammond, Detroit, Mich.: Emergency Cervical Mediastinotomy in a Case of Massive Mediastinal and Subcutaneous Emphysema Secondary to Removal of Foreign Body From the Bronchus.**—This case report is that of an 18-month-old infant who had choked on a piece of apple one and one-half hours prior to admission to the hospital. Physical examination and x-ray pictures demonstrated a check-valve obstruction of the left main bronchus. A 5 mm. bronchoscope was used and a portion of the foreign body was extracted with forceps, the remainder being expelled through the bronchoscope during a forced expiration. The infant left the operating room in good condition but twenty minutes later was in extremis due to massive mediastinal and subcutaneous emphysema. The emphysema extended from the head over the entire trunk and involved all four extremities. An immediate cervical mediastinotomy resulted in a release of considerable air under tension and the emphysema gradually disappeared. The infant was discharged from the hospital on the sixteenth postoperative day.

**Leighton F. Johnson, Boston, Mass.: Bilateral Pneumothorax in a Tracheotomized Infant.**—An 8-month-old infant who had been tracheotomized six weeks previously for streptococic laryngitis at another hospital was admitted to Massachusetts Memorial Hospital for decannulization. An unsuccessful attempt to change the tube required an emergency reincision of the tracheostomy which was followed by a bilateral pneumothorax. Needles were inserted into both pleural cavities immediately, releasing 600 c.c. of air and this was followed by the resumption of normal respiration. X-ray pictures revealed prompt re-expansion of the lung. The infant completely recovered and, following laryngeal dilatation, was decannulated.

**Louis H. Clerf, Philadelphia, Pa.: Tracheopathia Osteoplastica (Osteoma of the Trachea).**—Clerf reviews the previously reported cases of bony tumors of the trachea and adds two cases that have come under his observation. They presented symptoms of hemoptysis and intermittent dyspnea. One patient had a long-standing history of bronchopulmonary and nasal infection whereas the only symptom in the second patient was that of severe recurrent hemoptyses. Bronchoscopic examination revealed ragged nodules and flakes of bone along the tracheal surface and these were found to be connected with the tracheal rings. The posterior wall was free from nodules. Histologic examination of nodules removed with forceps demonstrated them to be composed of bone.

**Frederick T. Hill, Waterville, Me.: Adenoma of the Bronchus, Treated by Coagulation.**—In this case report Hill presents a patient who had been subject to repeated pulmonary infections, supposedly pneumonia. These were complicated by severe attacks of hemoptysis, and bronchoscopic examination demonstrated a tumor of the right lower lobe which proved to be a bronchial adenoma. Therapy has consisted of electrocoagulation which has completely cleared the bronchus and

given complete relief of symptoms. In the discussion Louis Clerf, Philadelphia, mentioned a patient who had had an adenoma and has now developed a nodule in the opposite lung, the nature of which has not yet been determined.

**Paul H. Holinger, Chicago, Ill., H. James Hara, Hinsdale, Ill., and Edwin F. Hirsch (by invitation), Chicago, Ill.: Bronchogenic Carcinoma: An Analysis of 175 Proved Cases.**—A statistical analysis of etiology, symptomatology, pathology, and means of diagnosis is made of this series of 175 proved cases of bronchogenic carcinoma. The most reliable means of establishing a tentative diagnosis was considered to be by x-ray, while bronchoscopy was found to be the most reliable means of establishing a positive diagnosis. In 8 per cent of the cases more than one year elapsed between the initial symptoms and bronchoscopy. In 42 per cent six months to one year elapsed, and in the remaining 50 per cent less than six months elapsed. In 78 per cent of cases a positive bronchoscopic biopsy was obtained. The carcinoma was found on the right side in 111 of the cases and on the left in 60, while in 4 cases it was bilateral. In character, 64 per cent of the tumors were squamous cell, 17 per cent small round cell carcinomas, 13 per cent anaplastic carcinoma, and 6 per cent adenocarcinoma. The technique of bronchoscopic biopsy and criteria of operability are discussed. Therapy is considered surgical in every possible instance, but in cases unsuitable for surgery palliative irradiation or bronchoscopically applied radium or radon is mentioned.

**F. W. Davison, Danville, Pa.: Does Chronic Sinusitis Cause Bronchiectasis?** Davison points out that while chronic sinusitis and bronchiectasis are often found in the same patient, this does not mean that one infection is the cause of the other. Of fifty patients with bronchiectasis, Davison found that 72 per cent developed their bronchiectasis during the first decade of life, 74 per cent of these tracing the onset of their chronic cough to an acute bronchopulmonary infection. Davison showed that mucosal edema of 1 mm. in a 6 mm. bronchus reduced the size of the lumen 42 per cent, while the same amount of edema reduced a 3 mm. bronchial lumen of a child to 11 per cent of its original airway. It was felt that mucosal edema was probably the chief factor responsible for the atelectasis which led to the development of the bronchiectasis. He attributes this mucosal edema to an allergic or hypersensitive state and noted that the allergic or hypersensitive state was an etiologic factor of bronchiectasis in 80 per cent of his series of fifty patients with bronchiectasis. In comparing these patients with fifty patients with sinusitis, Davison notes that the patients with sinusitis and bronchiectasis are twice as numerous when an allergic factor can be demonstrated. He noted that thirty-three patients who had both sinusitis and bronchiectasis were of the allergic type, suggesting that excessive mucosal edema found in these hypersensitive individuals predisposed them to the development of sinusitis as well as to development of bronchiectasis.

**Chevalier L. Jackson and Charles M. Norris (by invitation), Philadelphia, Pa.: Anatomy of the Bronchial Tree and Lungs With a Simple Nomenclature.**—This presentation was an animated motion picture film in color correlating the endoscopic landmarks of the lobar and segmental bronchi with their corresponding lobes and segments. The positions and relations as well as the relative size and importance of various lobes and segments were shown, together with a diagrammatic representation of the endoscopic picture at various levels in the tracheobronchial tree. The nomenclature included terms selected on a basis of topographical relationship and conserved the clinical names of "apical" and "basal" for segments of the apex and base of the lung respectively. The lungs were subdivided according to their bronchial distribution with each lobar segmental bronchus taking the name of the lobe or segment to which it corresponded. In the discussion, **Herman Moersch, Rochester, Minn.**, suggested the adoption of the uniform nomenclature among the various groups interested in this specialty.

# Book Reviews

---

**Industrial Ophthalmology.** By Hedwig S. Kuhn, M.D. Ed. 1, pp. 294, with 114 illustrations. St. Louis, 1944, The C. V. Mosby Company. \$6.50.

Dr. Kuhn has made a splendid contribution to ophthalmic literature. She has at last given us a concise and well-illustrated monograph that can and will be accepted as an authoritative reference book by all interested in industrial ophthalmology. She has added dignity and meaning to the term Industrial Ophthalmologist, and the term Company Oculist should soon vanish.

The chapter on Visual Testing in Industry gives a plan of placing employees in industry where their visual skills indicate they should be. She describes in detail the use of the new orthorater visual screening tests in industry. This is an instrument which can be operated by a technician, and the records kept by a punch-card system. This enables the ophthalmologist to pick out the employees with glaring visual defects without laboriously examining every employee. Other tests are discussed and their advantages pointed out.

The chapter on Correction of Visual Defects, as they relate to the patient's job, should interest all ophthalmologists because it presents many practical applications which can be used in everyday practice as well as in industry.

The chapter on Industrial Eye Injuries Caused by Solid Bodies was contributed by Dr. Albert C. Snell of Rochester, N. Y. It is full, yet concise and to the point, giving many of Dr. Snell's common sense rules for handling the various types of ocular injuries. To those of us who know Dr. Snell, we realize that he has no peer in this field, having devoted many years of a long and useful life to this subject, both as a teacher and a practitioner.

The chapter on Goggles and Eye Protection is complete and well illustrated. It gives a method with concrete suggestions as to how a successful goggle plan can be instituted and operated for the protection of eyes in large industrial plants.

The last chapter is devoted largely to recent developments, such as "flash burns" and epidemic keratoconjunctivitis, with suggestions as to management and treatment. The section on Illumination should be read and reread both by labor and management, as well as by the ophthalmologist.

## Books Received

The receipt of books is acknowledged in this section and this treatment must be regarded as sufficient acknowledgement of the courtesy of the senders. Selections will be made for more extensive review dictated by the interests of our readers and as space permits.

**VASCULAR RESPONSES IN THE EXTREMITIES OF MAN IN HEALTH AND DISEASE.** By David I. Abramson, M.D., Captain, A. M. C., Cardiovascular Research, May Institute for Medical Research of the Jewish Hospital, Cincinnati. Cloth. Price \$5.00. Pp. 412, with 52 illustrations. Chicago, 1944, University of Chicago Press.

**TROPICAL NURSING—A HANDBOOK FOR NURSES AND OTHERS GOING ABROAD.** By A. L. Gregg, M.A., M.D., Hospital for Tropical Diseases, London Westminster Hospital Medical School. Cloth. Price \$3.00. Pp. 185, no illustrations. New York, 1944, Philosophical Library, Inc.

**VIRUS DISEASES IN MAN, ANIMAL, AND PLANT.** By Gustav Seifert. Cloth. Price \$5.00. Pp. 332, no illustrations. New York, 1944, Philosophical Library, Inc.

**SMALL COMMUNITY HOSPITALS.** By Henry J. Southmayd, Director, Division of Rural Hospitals, The Commonwealth Fund, New York City; Geddes Smith, Associate. Cloth. Price \$2.00. Pp. 182, with 4 illustrations. New York, 1944, Commonwealth Fund.

**PRACTICAL MALARIA CONTROL.** By Carl E. M. Gunther, M.D., Field Medical Officer, Australian Medical Corps. Cloth. Price \$2.50. Pp. 91, no illustrations. New York, 1944, Philosophical Library, Inc.

**SURGICAL CLINICS OF NORTH AMERICA, REPARATIVE SURGERY.** By many contributors. Cloth. Pp. 490, with 141 illustrations. Philadelphia, 1944, W. B. Saunders Company.

**THE AMERICAN ILLUSTRATED MEDICAL DICTIONARY.** By W. A. Newman Dorland, A.M., M.D., F.A.C.S., Lieutenant-Colonel, M. R. C., U. S. Army, in collaboration with E. C. L. Miller, M.D., Medical College of Virginia. Leather. Price \$7.00, plain; \$7.50, thumb-indexed. Pp. 1668, with 885 illustrations. Philadelphia, 1944, W. B. Saunders Company.

**MINOR SURGERY.** By various authors. Edited by Humphry Rolleston and Alan Moneriff. Cloth. Price \$5.00. Pp. 174 with 30 illustrations. New York, 1944, Philosophical Library, Inc.

**TECHNIQUE IN TRAUMA.** By Fraser B. Gurd, M.D., C.M., and F. Douglas Ackman, M.D., C. M., Montreal General Hospital and MacGill University. Cloth. Price \$2.00. Pp. 68, with 3 illustrations. Philadelphia, 1944, J. B. Lippincott Company.

**TREATMENT OF PEPTIC ULCER.** By George J. Heuer, M.C., Professor of Surgery, Cornell University Medical College, and Surgeon-in-Chief of New York Hospital. Cloth. Price \$3.00. Pp. 118, no illustrations. Philadelphia, 1944, Barbara Whitney Henry Fund, J. B. Lippincott Company.

**DENTAL TREATMENT OF MAXILLO-FACIAL INJURIES.** By W. Kelsey Fry, M.C., M.R.C.S., L.R.C.P., Consulting Dental Surgeon to the R. A. F., Consulting Dental Surgeon to Ministry of Health and to Guy's Hospital; and others. Cloth. Price \$6.50. Pp. 434, no illustrations. Philadelphia, 1944, J. B. Lippincott Company.

**INFECTIONS OF THE PERITONEUM.** By Bernhard Steinberg, M.D., Director of Toledo Hospital Institute of Medical Research; Past Fellow of National Research Council; Former Crile Research Fellow, Western Reserve University. Cloth. Pp. 454, with 45 illustrations. New York, 1944, Paul B. Hoeber, Inc.

**INTRAVENOUS ANESTHESIA.** By R. Charles Adams, M.D., C.M., M.S. (Anesthesiology), Associate in Section on Anesthesiology, Mayo Clinic; Instructor in Anesthesiology, Mayo Foundation. Cloth. Price \$12.00. Pp. 663, with 73 illustrations. New York, 1944, P. B. Hoeber, Inc.

**THE NEUROSURGICAL PATIENT.** By Carl W. Rand, Professor of Neurological Surgery, University of Southern California, School of Medicine, Los Angeles, Calif. Cloth. Price \$4.00. Pp. 576, with 121 illustrations. Springfield, Ill., 1944, Charles C Thomas, Publisher.

# SURGERY

VOL. 16

OCTOBER, 1944

No. 4

## Original Communications

### THE PROGNOSIS IN ACUTE HEMATOGENOUS OSTEOMYELITIS WITH AND WITHOUT CHEMOTHERAPY

WILLIAM E. KENNEX, M.D., NEW HAVEN, CONN.

*(From the Department of Surgery, Section of Orthopedics, Yale University School of Medicine)*

#### INTRODUCTION

**D**URING the course of time, progress in the therapy of a disease is expected. Whether improvement has in fact been made rests upon the comparison of the results obtained in the present with those of the past.

It is reasonable to suppose that the addition of the sulfonamides to the treatment of acute hematogenous osteomyelitis may have altered certain features of this disease. Therefore it was deemed advisable to study various large series of cases reported in the literature both before and after the use of the sulfonamide drugs. In this manner a general standard for the past could be reached against which the results of treatment with the new drugs might be compared now and in the future.

Mortality is naturally of prime concern and the local result of secondary importance. Consequently, the previous prognosis will be presented from the standpoints of mortality and of disability. An attempt will then be made to compare the present picture with that of the past, special emphasis being placed on the methods of treatment: operative, supportive, nonoperative, and chemotherapeutic.

#### MORTALITY WITHOUT CHEMOTHERAPY

Without chemotherapy, the average mortality was 23 per cent. In Table I are listed the figures given by several authors for their respective series.

TABLE I

AUTHORS	NO. OF CASES	OVERALL AVERAGE MORTALITY (%)
Pyrah and Pain <sup>24</sup>	262	27.1
Doran and Brown <sup>9</sup>	42	19.0
Fraser <sup>11</sup>	56	23.2
Crossan <sup>8</sup>	121	21.4
Findlay <sup>10</sup>	50	24.0
Mahorner <sup>18</sup>	112	25.2
Robertson <sup>25</sup>	337	22.0
Butler <sup>6</sup>	500	25.4
Penberthy and Weller <sup>23</sup>	67	22.8
Total	1547	

However, if these cases were divided into toxic and nontoxic, the average mortality for the former was 46 per cent. Toxic refers to patients with a temperature of 103°F. or higher, or to those with a high number of colonies of organisms recoverable per unit of blood. The standard varied somewhat with the individual reporting the series. Table II is illustrative of the findings of a few authors.

TABLE II

AUTHORS	NO. OF CASES	MORTALITY IN TOXIC CASES (%)
Mahorner <sup>18</sup>	60	50.0
Baker <sup>2</sup>	33	66.6
McCoy and Ross <sup>21</sup>	10	60.0
Beekman and Sullivan <sup>3</sup>	--	46.0
Crossan <sup>8</sup>	34	53.0
Brown <sup>5</sup>	77	33.6
Total	214	

It is to be noted that such figures approach septicemic mortality.

Certain features became clear with reference to the time of the operative procedure. Crossan<sup>8</sup> found that if operation were carried out within the first seven days of the disease, the mortality was between 34 and 39 per cent. It fell to 8 per cent during the eighth to the tenth days and to 0 per cent on the eleventh to the fourteenth days. It rose again thereafter. Wilson<sup>27</sup> reported a mortality of 25 per cent for those operated upon during the first seven days of the disease, and 9.7 per cent for the group treated operatively from the seventh to the twenty-eighth days. Mahorner and Crain<sup>18, 19</sup> pointed out that there was no mortality in their series if operation were performed within forty-eight hours of the onset of symptoms. However, there was a 35 per cent mortality during the third to the seventh days, and 13.3 per cent thereafter. A very significant additional observation was that there were no deaths if the patients had been hospitalized for four days before operation. This could be taken as an indication of the value of preoperative preparation. Beekman and Sullivan<sup>3</sup> found a 23 per cent mortality in a group operated upon within the first week of the disease and 8.9 per cent afterwards.

Consequently, it became clear that operation\* in the first week of the disease was accompanied by a prohibitive mortality. Certainly it is plausible that before the seventh day the infection had not been sufficiently well localized to prevent an overwhelming septicemia following operative disturbance.†

Crossan<sup>8</sup> found that operation before the seventh day carried a mortality of 53 per cent if the temperature were 102° F. or more. Mahorner and Crain<sup>18, 19</sup> reported a 48.6 per cent mortality for operation before the seventh day on those with a temperature of 103° F. or more. These figures for the so-called toxic cases approach those of septicemia not associated with osteomyelitis.

On the other hand, even when the patient appeared extremely ill, operation after the seventh day yielded a mortality of 25 per cent (Crossan,<sup>8</sup> compare with 53 per cent) or of 20 per cent (Mahorner,<sup>18, 19</sup> compare with 48.6 per cent). This is evidence that before the seventh day the infection is not localized, and that *early* operation, especially upon either an unprepared or a toxic individual is dangerous.

Analysis was then made of the type of procedure performed. Drilling or guttering‡ the bone, whether such procedures were done as early or as delayed operations, seems to make little or no difference to the mortality percentages. (See Table III.) The severity of the disease in the individual patient does however make a striking difference. (See Table IV.)

TABLE III\*

	NO. OF CASES	MORTALITY (%)
Crossan <sup>8</sup> Immediate guttering	32	31
Immediate drilling	18	33
Delayed guttering	15	26
Delayed drilling	14	28
Total	79	

\*Reproduced in part and with slight modifications by permission of the authors and of the *Annals of Surgery*.

This leaves an average mortality of 33.6 per cent for bone operations on toxic patients and a figure of 2.2 per cent for the same procedures on nontoxic patients.

Therefore, prior to chemotherapy, it was wise to delay bone decompression several days. This was in order (1) to restore the fluid balance, (2) to control the septicemia, (3) to allow granulation to wall off the osteomyelitic focus, and (4) to avoid a fatal septicemia as a result of operative interference.

\*Except upon those who had received several days of preoperative supportive therapy.

†It is well realized that there may be a vast difference in time between the onset of symptoms and operation on the one hand, and the day of admission and operation on the other hand. In some series the former is used, in others the latter, and at times neither is given. The end results may be influenced by this time factor and therefore an attempt has been made in this communication to reduce all that are feasible to the duration between the onset of symptoms and the operation.

‡Guttering refers to that procedure in which a large amount of cortical bone is removed exposing widely the medullary cavity.



TABLE IV\*

		NO. OF CASES	MORTALITY (%)
Brown <sup>5</sup>		<i>Toxic Cases</i>	
	Immediate guttering	35	31.4
	Immediate drilling	24	45.8
	Delayed guttering	8	37.5
	Delayed drilling	10	20.2
	Total	77	
Brown <sup>5</sup>		<i>Nontoxic Cases</i>	
	Immediate guttering	16	6.2
	Immediate drilling	9	0.0
	Delayed guttering	34	2.9
	Delayed drilling	6	0.0
	Total	65	

\*Reproduced in part and with slight modifications by permission of the authors and of the Annals of Surgery.

#### LOCAL RESULTS WITHOUT CHEMOTHERAPY

Whether early operation were necessary for the later integrity of the bone was, and still is seriously questioned. Unfortunately authors have hitherto been so concerned with the mortality that little has been written comparing the functional results of early and of delayed operations. One of the strongest pleas for early intervention in order to avoid chronic osteomyelitis, persistent sinuses, recurrences, shortening, deformities, and limitation of motion of neighboring joints comes from McCarroll and Key.<sup>20</sup> In 200 cases of chronic osteomyelitis they found that only 9 patients had been operated upon within one week of the onset of symptoms. That most certainly indicates that the longer operation is delayed the more surely sequelae will occur. In a report by Harris,<sup>14</sup> of a small number of cases, healing took place in 13 out of 17 patients surviving early\* bone decompression, whereas it occurred in only 1 of 12 survivals when operation was delayed until after the seventh day. Doran and Brown<sup>9</sup> stated that the majority of their patients receiving early care recovered within an average of four months. In fourteen patients treated by bone decompression within a few days of onset of symptoms, healing took place in an average of four months. Of twenty patients treated later than a few days after onset, healing took place in 14 and did not occur in 6. The average length of time for healing in these cases must have been much greater since for the whole series of 34 cases, the average time for healing was 11.4 months (in contrast to four months for patients getting early care).

In Butler's series,<sup>6</sup> bone decompression in 155 cases yielded complete healing in 55 per cent whereas draining of a subperiosteal abscess in 52 cases gave good results in only 41 per cent.

Such experiences prove not only the wisdom of bone decompression but also the desirability of such a procedure early in the course of the disease.

\*That is within seven days of onset of symptoms.

It is reasonable to believe that the longer the infection is allowed to persist in bone, the greater the destruction, the more extensive the process, and the poorer the end result is likely to be. Therefore, if early operation could be performed with a low mortality, one should expect a better prognosis for the local lesion.

However, regardless of the time or type of operation, the overall end results before sulfonamide therapy, expressed approximately, were as follows: Healing took place in 50 per cent of the cases; metastasis occurred in 33 per cent, and sequestration in 33 per cent. About one-third of the patients had either lengthening or shortening of the extremity, limitation of motion, or ankylosis of the neighboring joint.

Many reported series include patients who were treated by incision down to bone alone, by aspiration alone, or by no operative procedure. The mortality for those (toxic and nontoxic) receiving incision alone without sulfonamide is 14 per cent (on the basis of 359 collected cases). Three hundred and nine have follow-ups which reveal that 181 (or almost 60 per cent) are unsatisfactory. Some had metastases, others had some type of disability, or needed sequestrectomy, diaphysectomy, or were unhealed. There is a striking difference in the end result as far as the bone is concerned between incision and that of decompression.

Patients treated with aspiration alone without chemotherapy had a mortality of 12 per cent. In a follow-up of 96, there were poor results in 47 or almost 50 per cent. Furthermore, of the 96 total, 41 had spontaneous drainage although this was not considered per se reason enough to classify it as a poor outcome. The end result is far from desirable although the small number of cases prevents any conclusions.

Consequently, the method most likely to offer a reasonable hope of avoiding disability is that of early operation in the nature of bone decompression. However desirable it may have been to use this method of therapy, the high mortality of early operation without the sulfonamide drugs prevented its adequate application.

#### MORTALITY WITH CHEMOTHERAPY

When the appropriate sulfonamide was administered systemically the average mortality fell from the previously found figure of 23 to 3.5 per cent. (See Table V.)

TABLE V  
WHEN SULFONAMIDE WAS USED SYSTEMICALLY

AUTHORS	NO. OF CASES	MORTALITY (%)
Baker <sup>2</sup>	9	11.0
Penberthy and Weller <sup>23</sup>	19	0
Wilson and McKeever <sup>29</sup>	31	3.2
L'Episcopo and Hagerty <sup>17</sup>	27	3.7
Total	86	

Undoubtedly this represents a decided improvement in prognosis, inasmuch as the overall mortality fell to that of the nontoxic group without chemotherapy.

#### LOCAL RESULTS WITH CHEMOTHERAPY

Although sufficient time has not elapsed since the use of sulfonamides to allow an adequate follow-up on a large group of cases, the following facts are of some significance.

In a group of 47 patients treated by delayed bone decompression and by sulfonamide systemically, results in 18 were unsatisfactory.

L'Episcopo and Hagerty<sup>17</sup> reported a series of 27 cases; in 15 patients aspiration was done, in 4 incision to bone only, and 8 were untouched. They were treated by rest, soaks, and chemotherapy, in the main. In 5 drainage was spontaneously, 4 had exacerbations, and metastases occurred 4 times. Eight patients developed sequestrae, 1 had a pathologic fracture, and 4 had some functional impairment of adjacent joints. Therefore neither delayed bone decompression, simple incision, nor aspiration seem productive of good results even after the use of the sulfonamide drugs.

Bick<sup>4</sup> concluded that the sulfonamides had not altered the general course of the pathologic process in bone, the rate of recurrences, or metastases. Wilson and McKeever<sup>29</sup> were undecided as to whether chemotherapy favorably influenced the change in the bone. They felt that there were fewer examples of massive bone destruction, and that healing occurred more rapidly. According to these authors metastasis was about one-half as frequent as before the sulfonamide drugs.

Chemotherapy, therefore, has had as its major effect the reduction of the mortality by controlling the primary septicemia and that following operation. It has perhaps to a minor degree aided wound healing, and may prove in the future to have reduced the incidence of metastasis. It has had no appreciable effect on the bone. The greatest advantage of the sulfonamides, however, would appear to be that now early bone decompression can be performed safely. Certainly by the use of infusions, intravenous chemotherapy, and adequate sedation almost all patients can be prepared for decompression within twelve hours. Under these circumstances, a low mortality and a much better local prognosis can be expected.

It will be noted that the entity of acute hematogenous osteomyelitis in infants as described by Green and Shannon<sup>12</sup> has been omitted from this discussion. They have pointed out the differences in the disease in infants. Acute hematogenous osteomyelitis in infants is usually caused by streptococci. The bone is relatively soft. The suppurative process more readily penetrates into the soft tissue. Absorption of the necrotic bone and reconstitution of bone are more easily accomplished and the infection in general is better tolerated.

If such cases are included among the group occurring after infancy the general results may appear better than when staphylococcal osteomyelitis is considered separately. Consequently, a sharp division must be made between these two vastly different types of the disease. The process behaves not unlike a soft tissue abscess and apparently can be treated as such, that is, by simple incision of a presenting abscess. It remains to be seen through future experience whether these cases can be treated by drug alone and without operative intervention.

#### SUMMARY

The mortality in acute hematogenous osteomyelitis before chemotherapy was 23 per cent on the average, 46 per cent in the toxic cases, and around 3 per cent in the nontoxic cases. After sulfonamide the mortality was 3.5 per cent.

Previous to the use of the drug, early bone decompression was almost prohibited by the severe mortality. Yet early bone decompression yielded the best results from the standpoints of the later integrity of the bone and function of the limb.

Neither incision down to bone, aspiration, or withholding operation either before or after the sulfonamides has given as satisfactory results as early bone decompression.

The new drugs, by controlling the initial septicemia and that which may follow operative intervention, have now allowed safe, early procedures.

The sulfonamide drugs have not proved of value so far as the local pathologic process is concerned.

One must still depend upon operation for the best results.

This study has been based on the reported experiences of surgeons with 3,176 cases of acute hematogenous osteomyelitis.

Acknowledgement is gratefully made to Dr. Samuel C. Harvey and to Dr. Malcolm S. Eveleth, Department of Surgery, Yale University School of Medicine, for advice in the preparation of this report.

#### REFERENCES

1. Amberg, S., and Ghormley, R.: Osteomyelitis Among Children, *J. Pediat.* 5: 177-193, 1934.
2. Baker, L. D.: Acute Osteomyelitis With Staphylococcus Septicemia, *South. M. J.* 34: 619-627, 1941.
3. Beekman, F., and Sullivan, J. E.: Blood-borne Pyogenic Infections of Bones and Joints, *Ann. Surg.* 111: 292-314, 1940.
4. Bick, E.: Sulfone Chemotherapy in Hematogenous Osteomyelitis, *Surg., Gynec. & Obst.* 72: 995-1002, 1941.
5. Brown, H. P., Jr.: Acute Hematogenous Osteomyelitis of the Long Bones, *Ann. Surg.* 109: 596-614, 1939.
6. Butler, E. C. B.: The Treatment, Complications, and Late Results of Acute Hematogenous Osteomyelitis, *Brit. J. Surg.* 28: 261-274, 1941.
7. Cleveland, M.: Osteomyelitis and Pyogenic Infections of Joints, *Bull. New York Acad. Med.* 17: 205-220, 1941.
8. Crossan, E. T.: The Conservative Treatment of Acute Hematogenous Osteomyelitis, *Ann. Surg.* 103: 605-612, 1936.
9. Doran, W. T., and Brown, L.: Haematogenous Osteomyelitis, *Surg., Gynec. & Obst.* 40: 658-664, 1925.

10. Findlay, R. T.: Acute Osteomyelitis in Children, New York State J. Med. 36: 1231-1236, 1936.
11. Fraser, J.: Acute Osteomyelitis, Brit. M. J. 2: 539-541, 1934.
12. Green, W. T., and Shannon, J. G.: Osteomyelitis of Infants, Arch. Surg. 32: 462-493, 1936.
13. Haldeman, K. O.: Acute Osteomyelitis, Surg., Gynec. & Obst. 59: 25-31, 1934.
14. Harris, C. T.: Acute Osteomyelitis, New York State J. Med. 39: 1554-1557, 1939.
15. Hoyt, W. A., Davis, A. E., and Van Buren, G.: Acute Hematogenous Staphylococcal Osteomyelitis, J. A. M. A. 117: 2043-2050, 1941.
16. Johnston, R. A. Y.: Effect of Inflammation on the Epiphyses, Arch. Surg. 32: 810-822, 1936.
17. L'Episcopo, J. B., and Hagerty, E. D.: Conservative Management of Acute Osteomyelitis, New York State J. Med. 43: 853-856, 1943.
18. Mahorner, H. R.: Delayed Operation for Acute Hematogenous Osteomyelitis, New Orleans M. & S. J. 90: 121-130, 1937.
19. Mahorner, H., and Crain, A. P., Jr.: Acute Hematogenous Osteomyelitis, Ann. Surg. 115: 790-815, 1942.
20. McCarroll, H. R., and Key, J. A.: The Present Status of Chronic Osteomyelitis, Surg., Gynec. & Obst. 68: 1007-1016, 1939.
21. McCoy, R. H., and Ross, D. E.: Acute Haematogenous Osteomyelitis, Canad. M. A. J. 42: 162-168, 1940.
22. McKeown, K. C.: The Conservative Treatment of Osteomyelitis, Proc. roy. Soc. Med. 35: 215-217, 1942.
23. Penberthy, G. C., and Weller, C. N.: Chemotherapy as an Aid in the Management of Acute Osteomyelitis, Ann. Surg. 114: 129-146, 1941.
24. Pyrah, L. N., and Pain, A. B.: Acute Infective Osteomyelitis, a Review of 262 Cases, Brit. J. Surg. 20: 590-601, 1933.
25. Robertson, D. E.: Acute Hematogenous Osteomyelitis, J. Bone & Joint Surg. 20: 35-47, 1938.
26. Williams, S. W.: The Early Treatment of Acute Staphylococcal Osteomyelitis, M. J. Australia 2: 459-466, 1937.
27. Wilson, J. C.: The Delayed Operative Treatment of Acute Hematogenous Osteomyelitis, SURGERY 9: 666-674, 1941.
28. Wilson, J. C., and McKeever, F. M.: Hematogenous Acute Osteomyelitis in Children, J. Bone & Joint Surg. 18: 328-332, 1936.
29. Wilson, J. C., and McKeever, F. M.: The Role of Sulfonamide Drugs in the Treatment of Hematogenous Osteomyelitis, J. Bone & Joint Surg. 25: 41-48, 1943.

## EMBOLIC OCCLUSION OF MAJOR ARTERIES

JOHN T. REYNOLDS, M.D., AND FRANK J. JIRKA, M.D.  
CHICAGO, ILL.

(From the Department of Surgery, University of Illinois College of Medicine; from the Surgical Service of Dr. Frank J. Jirka, Cook County Hospital; and from the Fourth Surgical Service, St. Luke's Hospital)

**INTRODUCTION.**—Failure to counteract the ill effects of embolic occlusion of major arteries may result in the loss of limb. In spite of the fact that these embolic phenomena usually occur as a complication of an already serious cardiac disease, opinion today favors early operative removal of the embolus if such a procedure is possible. Embolectomy is preferred because it may save the extremity and because the strain of this operation is usually less than that of amputation. Every means must be used immediately if the embolectomy is to be successful in preventing the loss of the involved limb.

*Source of Emboli.*—The most common causes of emboli large enough to embarrass the peripheral circulation are rheumatic heart disease, arteriosclerotic (or hypertensive) heart disease, and the heart disease following occlusion of the coronary arteries. These emboli originate from mural thrombi which develop within the lumen of the heart. They occur concomitantly with a seriously decompensated myocardium or as a mural thrombosis whose nidus is laid down over myocardium infarcted by coronary artery occlusion. Emboli may form (see Case 7) from thrombi deposited on the intimal lesions of the great vessels. They may also form in arterial aneurysms and be swept into the periphery. "Paradoxical" emboli may occur.

Emboli of sufficient size to occlude major arteries are rare in the course of bacterial endocarditis. When they occur they arise from mural thrombi and are not valvular vegetations. Emboli from the valvular vegetations may indirectly lead to the formation of major embolic phenomena by producing pyogenic aneurysms which in turn give rise to peripheral emboli.

*Circulatory Factors.*—There is no information as to the factor or factors which initiate the scattering of emboli from a heart which has been fibrillating for a long time. Frequently the phenomenon is preceded and/or accompanied by physical exhaustion (Cases 13 and 16)

The heparin used in Case 8 was furnished by the Abbott Laboratories, North Chicago, Ill. All other heparin was furnished in the form of Liqueamin by Hoffmann-La Roche, Inc., Nutley, N. J., through the courtesy of Dr. Geza de Takats.

The Rhythmic Compressor used at the Cook County Hospital to administer continuous intermittent venous compression was made available to the authors by the courtesy of the Burdick Corporation, 737 North Michigan Avenue, Chicago, Ill.

Enlarged from a report delivered at a meeting of the Society of University Surgeons, Nashville, Tenn., Feb. 12, 1944.

Received for publication, May 20, 1944.

and/or infection (Case 13). The histories of these patients usually reveal a recent and severe change in some feature of the cardiac mechanism.

Many patients with severe myocardial decompensation are under hospital care at the time the peripheral emboli occur. Repeatedly the occurrence of emboli has been noted to occur concomitantly with a change of digitalis dosage. These patients often have been given intensive digitalis therapy in an attempt to bring about circulatory efficiency as rapidly as possible (Cases 11 and 13). There is frequent evidence of digitalis overdosage occurring prior to or synchronously with the development of an embolus (Cases 13 and 14). Some patients without decompensation may have had the digitalis dosage increased or they may have taken the drug voluntarily (Cases 2 and 6). This clinical observation of the tendency of digitalis to encourage thrombosis is supported by the recent experiments of deTakats, Trumpp, and Gilbert.

Patients with coronary artery occlusions may develop peripheral emboli without digitalis therapy. In this group the coronary disease itself has caused circulatory and contractile anomalies which are sufficient to give rise to emboli. Unrecognized coronary attacks may occur. In such cases diagnosis of disease other than cardiac may have allowed the patient to become falsely secure and his failure to rest may so tax the diseased myocardium that an embolus develops. There seems to be a tendency for such emboli to occur on or about the tenth day following coronary artery occlusion (Cases 3 and 8).

*Nature of the Embolus.*—The physical properties of the emboli are important for the final outcome of the disease. When small emboli are discharged, they usually lodge in small peripheral arteries, give rise to few symptoms, and may even remain undiagnosed. If they are followed by a large embolus, the peripheral gangrene which follows develops partly as a result of the large embolus and partly as a result of the smaller emboli.

Emboli are prone to lodge where the arterial lumen becomes smaller, that is, just above or at points of bifurcation. If the embolus is of such a nature that it does not further fragment, it remains at the point of impaction and gradually assumes the contour of the surrounding vessel. These emboli may be easily and completely removed (Fig. 1). However, if the embolus is forced into both branches of the bifurcating vessel so that it assumes a Y-like contour (Fig. 1), its removal is difficult even though the clot is compact and can be handled without fragmentation. It should be emphasized that complete removal of the clot in such cases is very important in order to assure every possible opportunity for collateral circulation to occur.

When the original embolus is friable, it frequently breaks up with liberation of numerous smaller emboli into the periphery. Gangrene is more frequently observed with multiple emboli than with a single embolus.

*The Physiologic Aspects of Embolic Occlusion.*—When an embolus lodges in an artery, the resultant pain is not due to stimulus to the intima. The pain usually does not occur simultaneously with the occlusion but develops some minutes later, usually following a period of paresthesia associated with a sense of cold in the affected area. Pain is present only when the occluded artery nourishes a predominantly muscular area and it is felt in this region. Lewis has suggested that the accumulation of muscular metabolites in the ischemic extremity is responsible for this pain.



Fig. 1 (Case 16).—The smaller embolus on the left was removed from the right femoral artery. The folded clot on the left was extracted from the level of the bifurcation of the left iliac artery and had to be forcefully removed to allow the portion of the clot which blocked the external iliac to be freed.

The artery immediately peripheral to the occlusion is always in spasm by the time direct observation of the vessel is possible. Such a spasm may be considered beneficial when, for instance, an embolus lodges at the femoral bifurcation and is thereby prevented from migrating to the popliteal region. The spasm together with the occlusion of the major arterial trunk results in marked ischemia at the periphery. The only blood supply to the occluded areas comes by collateral routes or by oozing around the embolus. Under such circumstances blood is rapidly carried away by the open venous channels, causing a serious blood want. The circulation is drastically slowed and the constricted vessels are filled with a column of blood at low pressure, which probably



is also exposed to increased amounts of thromboplastic material. This column of blood distal to the embolus is likely to clot, thus producing a thrombosis into the periphery from the original embolus. Under these circumstances the column of clotted blood distal to the embolus is called a tail thrombus. This clotted blood is limited to the lumen of the large artery just distal to the embolic occlusion. It may be extracted at the time of embolectomy if it has not extended into so many branches that it is thereby fixed in place or if it has not become so large that it has become adherent to the wall of the artery (Figs. 2, 3, and 4). Later

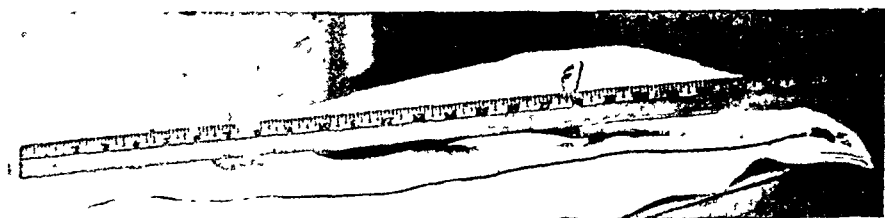


Fig. 2 (Case 6).—Embolus and tail thrombus removed. Note the length of the tail thrombus which, however, had not yet filled the arterial lumen.

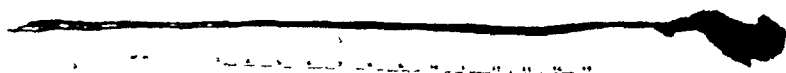


Fig. 3 (Case 20).—Embolus with tail thrombus. Note the greater diameter of the tail thrombus as compared with that in Cases 16 and 6.

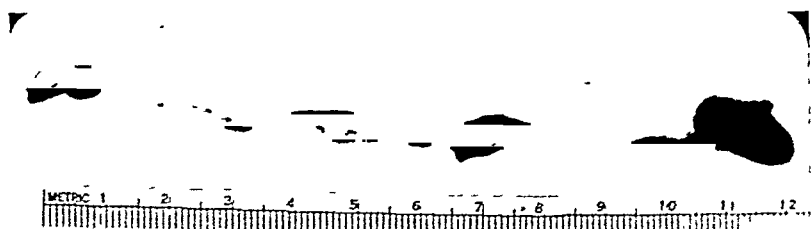


Fig. 4 (Case 19).—Note that the tail thrombus is about as large as the arterial lumen (as judged by the diameter of the original embolus at the right). Although the limb from which this thrombus was removed recovered, it is probable that if embolectomy had been delayed the entire arterial tree would ultimately have been plugged.

this process extending into the finer vessels may prevent any effective quantity of blood from reaching the periphery. When this has occurred, attempts to restore the circulation are obviously in vain and it is to the prevention of this phase of the process that therapeutic efforts are directed.

*Clinical Picture.*—The patient with a typical arterial embolus presents the initial symptom of paresthesia distributed in the area below the arterial occlusion, followed by a sense of cold and finally rapidly

developing pain distal to the occlusion and referred to the muscle area nourished by the vessel. This pain, which may be agonizing, is constant and is relieved by narcotics (occasionally by 100 per cent  $O_2$ , Rhoades). It is characteristically more severe when a large amount of muscle tissue is rendered ischemic, as occurs when a leg is involved, and less so when a smaller amount of muscle is involved, as in the arm. The paresthesia and sense of cold do not usually cause the patient to complain since they are rapidly succeeded by pain of such a degree that the patient seeks help. Pallor and a loss of peripheral motor power occur rapidly. This clinical picture is usually apparent within one-half an hour.



Fig. 5 (Case 6).—Photograph taken one hour after embolectomy of the right femoral artery. The pallor of this leg is still visible although less than it was preoperatively. The pallor is in contrast to the mottled appearance of the left leg which developed an embolus twenty-four hours previously. Neither of these limbs can be judged as beyond recovery by the appearance.

It should be emphasized that pain is not present over the embolus during the early stages of the process (Case 22). An embolus becomes tender only after arterial inflammation occurs about it. Although the length of time required for this to develop varies, it usually does not develop for several days.

When emboli move from one position to another, there is a change in the clinical picture, and pulses, previously closed, may be found to be open. Occasionally reflex arterial spasm may simulate embolic occlusion. This is usually recognizable when an artery previously not pulsating is found to be actively pulsating. Sometimes small peripheral emboli initiate immediate mass vasospastic phenomena which disappear spontaneously. Patients are seen in whom both femoral arteries are pulseless and the legs cold and useless; within a short time there may be complete regression of symptoms with no residual signs. On such an occasion the lack of pulsation originally noted must be interpreted as being due to spasm, since it is difficult to visualize an embolus large enough to occlude the aorta which would pass into the peripheral circulation without occluding a major vessel.

It may be necessary occasionally to differentiate between arterial embolus and a spontaneous arterial thrombosis. In the latter, the presence of long-standing arterial disease (intermittent claudication syndrome) may indicate the nature of the lesion. There also may be a question of differential diagnosis when acute thrombophlebitis of the femoral or iliac vein occurs with great rapidity. Unless there is a pronounced associated arterial spasm, this is not difficult.

*Therapy.*—When the diagnosis of arterial occlusion by embolus is made, the immediate and most important therapeutic objective is to restore the circulation. This is best done by preventing a thrombosis from occurring within the arterial system distal to the embolus until the removal of the embolus can be carried out, which should be done as rapidly as possible. Since occlusion of the terminal arteries and arterioles by thrombosis peripheral to the embolus may render all subsequent therapeutic efforts futile, heparin should be administered at once to arrest progressive arterial thrombosis. Operative intervention must then be considered.

*Anticoagulants:* In the last six patients of our series, heparin has been given preoperatively. In two of these, a tail thrombus was found. The removal of clots from the iliac bifurcation in these patients required that the vessel be open and subject to manipulation for about twenty minutes. At no time did thrombosis occur at the operative site in contrast to previous operations in which heparin had not been used. Contrary to what might be expected, the use of heparin was not associated with troublesome bleeding from capillary ooze. Small vessels were secured with ligatures and the incision in the arterial wall stopped bleeding with promptness when sutured.

*Relaxation of Arterial Spasm:* The relief of the arterial spasm that accompanies embolism has been the object of a variety of therapeutic procedures. It has become routine to give antispasmodics as soon as diagnosis is made, and papaverine may well be given at the same time as is the heparin. Papaverine does not produce as profound a release of spasm as does sympathetic block. Relief of the arterial spasm has played an important part in the therapy because the spasm has been considered to be undesirable. It is our opinion that the release of arterial spasm by sympathetic block may allow the embolus to pass from a major artery where surgical intervention is practicable into a peripheral artery or arteries where removal is no longer possible. This occurred in one patient (Case 9) in whom the spasm was apparently released by the spinal anesthetic used. The original occlusion was present three inches below the inguinal ligament. After the anesthetic was effective, exposure of the artery at that point showed it to be patent and pulsating. An embolus had undoubtedly moved into the popliteal region since the patient required an amputation for the gangrene of the foot which followed. Had this embolus been removed while in the

femoral artery, her recovery might have eventuated. In another patient (Case 13) the embolus descended from the aortic bifurcation to the femoral and iliac arteries after sympathetic block. Fortunately the embolus did not continue into the popliteal region.

It is our opinion that sympathetic block should not be done preoperatively in embolic occlusions of the aorta or iliac or femoral arteries, where direct or indirect access to the occlusion is relatively easy. For the same reason spinal anesthesia should not be used. Although sympathetic block has reportedly given considerable relief of pain, the risk of loss of the embolus makes preoperative administration of narcotics a wise method of securing analgesia.

*Removal of Embolus.*—There are two major contraindications to early embolectomy. The first is related to the physical condition of the patient. For instance, a major operation such as the abdominal approach to the aorta or iliac vessels may be so formidable that it is unsafe. The use of a general anesthetic may impose too great a risk on the patient (Case 4). A position on the table which entails considerable effort in breathing, such as the prone position required for popliteal exploration, may be more than the patient with cardiac embarrassment can tolerate. Occasionally even the manipulation required to administer a sympathetic block will be excessive, as in Case 3. In these cases only such therapy as will not tax the physical reserves of the patient may be used. Fortunately, however, patients are rarely too ill to tolerate the simple approach to the femoral artery and frequently through this approach iliac and aortic occlusions may be reached and relieved.

The second contraindication to early embolectomy obtains when the arteries occluded are so small that closure of an arteriotomy wound would obliterate their lumina. Such arteries usually supply fields with rich collateral. Hence embolectomy of the tibial, radial, and ulnar arteries is unnecessary. Because of the rich anastomosis about the shoulder, embolectomy of the axillary and brachial arteries should be considered only after heparin and sympathetic block have proved inadequate as measured by ability to use the muscles of the forearm. When popliteal emboli occur, if they have not resulted in the loss of motor function of the calf muscles, the outcome is likely to be good. Central thrombosis in the artery may extend high enough to obliterate the collaterals which are supplying the calf. This occurred in two patients (Cases 14 and 23). For this reason heparin must be given when nonoperative measures are used as well as an adjunct to embolectomy.

After the diagnosis is established, heparin should be given and embolectomy should be performed as quickly as possible. It usually requires from two to three hours to corroborate the diagnosis and prepare for operation. Embolectomy after longer periods may be successful. In one patient (Case 1) the operation was performed twenty-seven hours after an embolus had lodged in a severely arteriosclerotic

It may be necessary occasionally to differentiate<sup>c</sup> between arterial embolus and a spontaneous arterial thrombosis. In the latter, the presence of long-standing arterial disease (intermittent claudication syndrome) may indicate the nature of the lesion. There also may be a question of differential diagnosis when acute thrombophlebitis of the femoral or iliac vein occurs with great rapidity. Unless there is a pronounced associated arterial spasm, this is not difficult.

*Therapy.*—When the diagnosis of arterial occlusion by embolus is made, the immediate and most important therapeutic objective is to restore the circulation. This is best done by preventing a thrombosis from occurring within the arterial system distal to the embolus until the removal of the embolus can be carried out, which should be done as rapidly as possible. Since occlusion of the terminal arteries and arterioles by thrombosis peripheral to the embolus may render all subsequent therapeutic efforts futile, heparin should be administered at once to arrest progressive arterial thrombosis. Operative intervention must then be considered.

*Anticoagulants:* In the last six patients of our series, heparin has been given preoperatively. In two of these, a tail thrombus was found. The removal of clots from the iliac bifurcation in these patients required that the vessel be open and subject to manipulation for about twenty minutes. At no time did thrombosis occur at the operative site in contrast to previous operations in which heparin had not been used. Contrary to what might be expected, the use of heparin was not associated with troublesome bleeding from capillary ooze. Small vessels were secured with ligatures and the incision in the arterial wall stopped bleeding with promptness when sutured.

*Relaxation of Arterial Spasm:* The relief of the arterial spasm that accompanies embolism has been the object of a variety of therapeutic procedures. It has become routine to give antispasmodics as soon as diagnosis is made, and papaverine may well be given at the same time as is the heparin. Papaverine does not produce as profound a release of spasm as does sympathetic block. Relief of the arterial spasm has played an important part in the therapy because the spasm has been considered to be undesirable. It is our opinion that the release of arterial spasm by sympathetic block may allow the embolus to pass from a major artery where surgical intervention is practicable into a peripheral artery or arteries where removal is no longer possible. This occurred in one patient (Case 9) in whom the spasm was apparently released by the spinal anesthetic used. The original occlusion was present three inches below the inguinal ligament. After the anesthetic was effective, exposure of the artery at that point showed it to be patent and pulsating. An embolus had undoubtedly moved into the popliteal region since the patient required an amputation for the gangrene of the foot which followed. Had this embolus been removed while in the

ment, no pulse is felt at the ligament or below. When the embolus has lodged at the bifurcation of the femoral artery, the pulsation of the common femoral may be palpated even through the adipose tissue of obese patients. Below this level oscillometric readings readily locate the site of the occlusion. There is a characteristic exaggeration of oscillations just above the site of occlusion (Fig. 9).

After administration of heparin, the incision is best made parallel to the artery, and the abdomen is left exposed for extension. Provisional ligatures are placed about the artery above and below the site of arteriotomy. The incision should preferably be made below the largest part of the distended artery, so that the blood pressure may force the embolus out of the incision. The disadvantage to an incision so placed is that the lower end of the incision may be over the part of the artery already narrowed by the origin of the profunda. The advantage lies in making

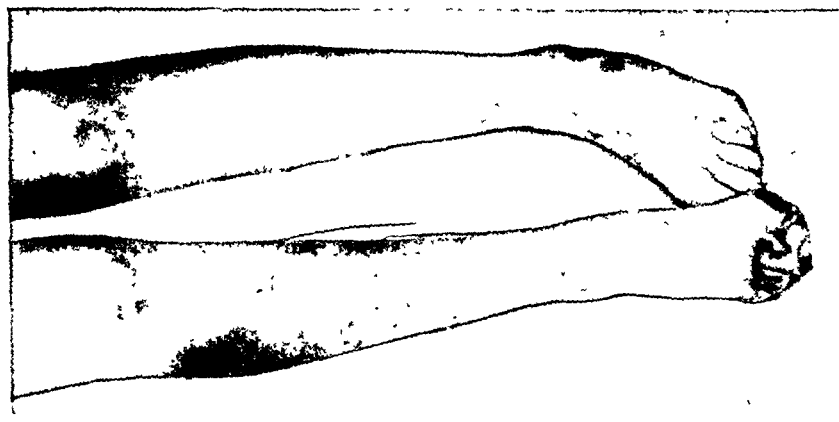


Fig. 8 (Case 13).—The right leg is beyond recovery. Note the dry gangrene of the toes and the patchy appearance of the anterior portion of the leg. This difference in viability of the leg is sometimes very distinct if one of the tibial arteries is closed and the other is open.

the incision into unaltered arterial wall. An incision so placed allows the removal of the tail thrombus, to be accomplished before removal of the main embolus. Removal of the tail thrombus would be difficult in the presence of a partially restored circulation. When the occlusion is above the level of the femoral bifurcation, the preferred site for arteriotomy is the common femoral artery at its broadest point, above the bifurcation, because closure of the arteriotomy will cause least narrowing of the lumen. Both provisional ligatures are then above the site of the major branches. Retrograde bleeding is thus more easily controlled. The distal artery is also kept closed to prevent fragments of emboli from passing down into the terminal branches.

If no blood flows from above when the artery is opened, it is assumed that the occlusion is below the iliac bifurcation. When a slow pulseless stream is seen, it may be due to retrograde bleeding by way of the iliac or epigastric arteries or to incomplete occlusion of the artery by the

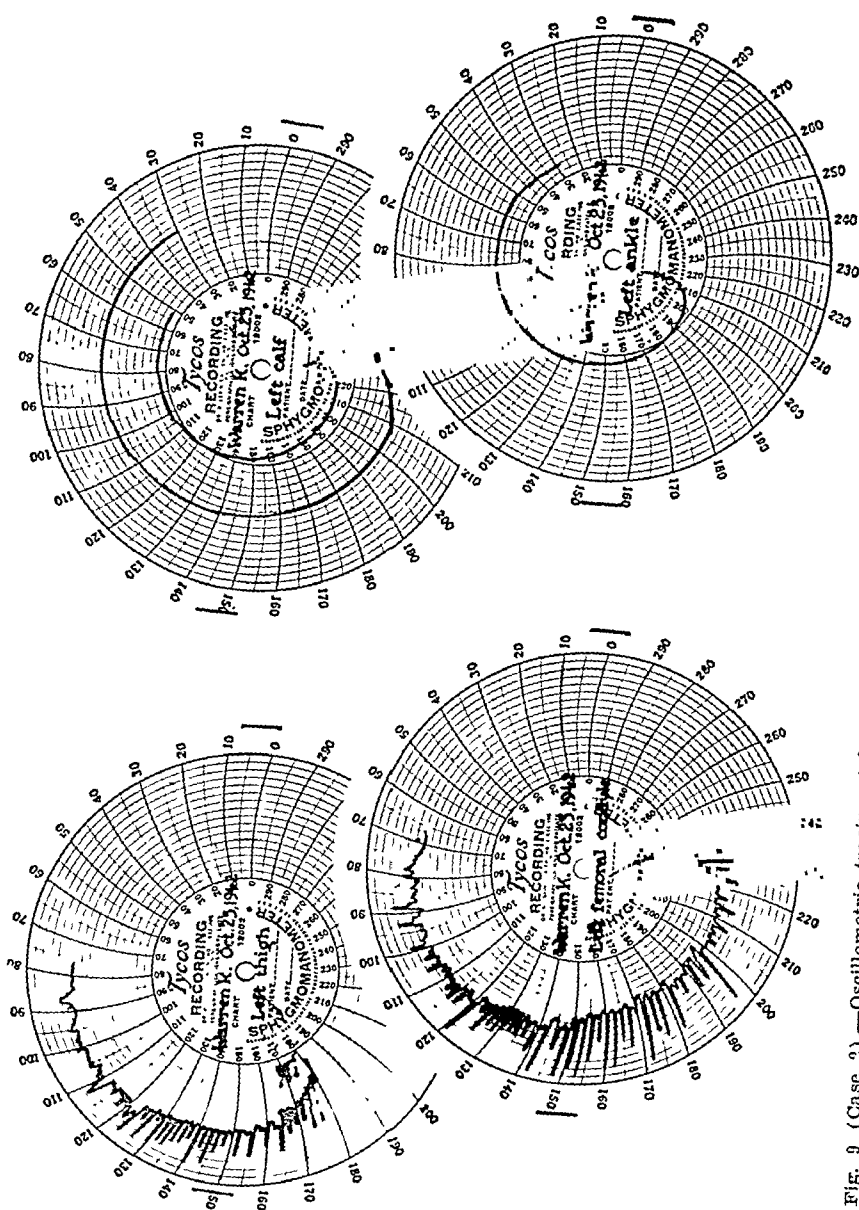


Fig. 9 (Case 2).—Oscillographic tracings taken on the day of occlusion of the left popliteal artery. Note the exaggerated oscillation of the artery just above the level of the occlusion and the absence of oscillation in the leg below it. See Fig. 11 for tracing taken fifteen months later.

embolus. In our experience the removal of the embolus from the region above the incision has not been easy. In one patient (Case 2), operated upon by Dr. de Takats, the first embolus in the left iliac artery was brought down by retroperitoneal arterial massage. In another (Case 11) the lowermost portion of the embolus was seen at the inguinal ligament and was grasped with gallstone forceps and extracted. The same procedure was used in Case 10. In Case 4 an actual incision into the iliac artery was used; the embolus was not obtained through the original incision and another higher incision was necessary. Subsequent experience would probably allow such an embolus to be removed through one incision, and that in the femoral artery. In Case 13 the right iliac was occluded at the level of the bifurcation; probing, passage of catheters (with and without suction), and milking failed to dislodge the embolus. The artery was in great spasm several times during the attempted embolectomy. This spasm was so great that it was hoped that the diagnosis had been wrong and that arterial spasm was the underlying pathologic change. However, there was no relief of circulatory obstruction by sympathetic block, and the leg became gangrenous. A patient (Case 16) whose left iliac was occluded in practically the same way was satisfactorily freed of the embolus when a gallstone probe was passed above the embolus, turned, and pulled down. The same procedure was used on two other patients (Cases 19 and 20). This maneuver apparently was successful because when the blunt end of the scoop which had been passed above the embolus was turned and removed, it engaged the embolus and pulled it out of the internal iliac where it was tightly wedged. The end of the scoop must not engage the arterial wall at the point of bifurcation when the clot is pulled out (Fig. 10). The same precaution applies to the use of any rigid probe with a knobby end. The possibility of pushing an embolus up to a bifurcation with resultant embolization of the other artery should not be forgotten.

In our experience the use of suction has not been successful, since it is impossible to apply the suction force directly to the embolus. Although we have had no experience with embolectomy on aortic occlusion, we would assume a similar difficulty.

Direct exposure of the iliac vessels with general anesthesia may provide satisfactory exposure. One patient (Case 4) was treated satisfactorily by embolectomy through an incision directly into the iliac vessel. However, this required a general anesthetic, and the death from "cardiac collapse" may have been influenced by such a major procedure. Subsequent iliac embolectomies have been successful using the femoral artery.

Free massive pulsating hemorrhage should be obtained before closure of the wound.

The suture material should be fine and nonabsorbable. Silk or cotton, preferably waxed to prevent cutting, has been used in the patients re-



ported here. Several autopsy specimens have revealed patent arteries at the site of incision.

The question of vein ligation at the time of embolectomy is a controversial subject. In the present series of cases concomitant vein ligation was performed nine times. In one patient (Case 11) marked redness and cyanosis of the leg occurred in the immediate postoperative period, but since the patient died in five days from the cardiac condition, it was impossible to correlate the vein ligation, the color of the leg, and the

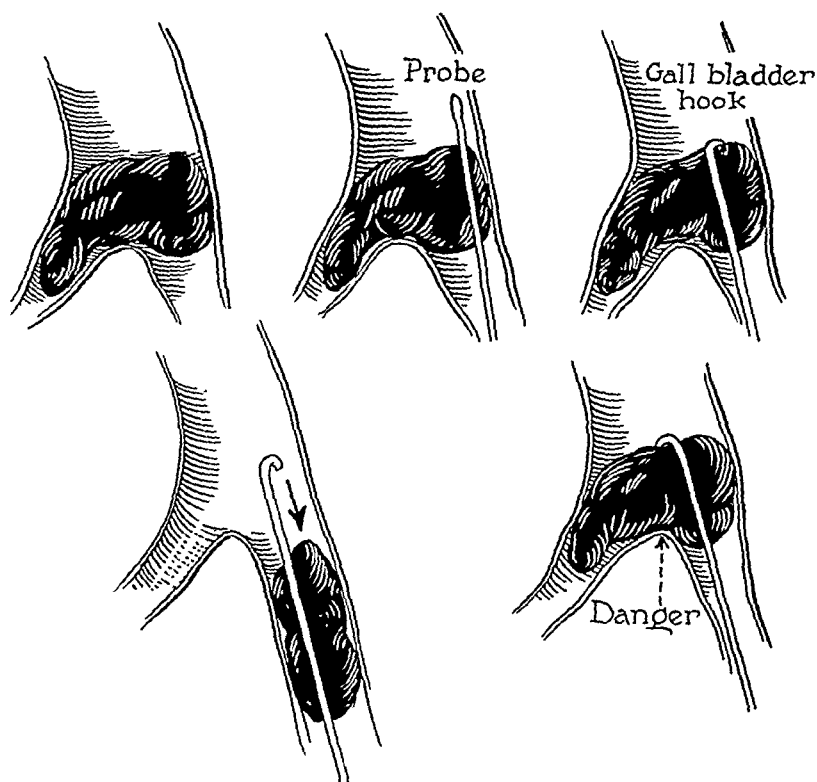


Fig. 10.—Illustration to emphasize the maneuver used to extract a clot from an artery where the clot has become wedged into the bifurcation and where the arteriotomy has been done below the level of the clot. Note that the end of the probe must be above the clot before it is turned and pulled down. Note also that the probe must be turned away from the direction of the major proximal branch.

final result to the limb. In seven of these patients the limb showed apparent total recovery as far as circulation was concerned, although six died in the immediate postoperative period. Only three required amputation and one of these developed inadequate circulation only very slowly after embolectomy (from seven to ten days). In the patient reported in Case 16, one vein was ligated and the other left unligated. After thirty-six hours, when she died from cardiac failure, both legs were equally warm and total recovery had apparently occurred. Thrombosis central to the ligated vein has not been seen. In our most recent cases vein ligation has been used only if there was serious doubt as to the

effectiveness of the arterial embolectomy. If the toes were not warm and the pulse had not returned and the patient still had considerable pain in the leg, the vein was ligated. This procedure follows the practice of Dr. Barney Brooks.

At the end of the operation the coagulation time should be determined and enough heparin given to bring it up to fifteen minutes, and heparin should be continued in dosages sufficient to maintain that coagulation time. Fifty milligrams of heparin every four hours have been found adequate to keep this level, although larger quantities may often be required. Smaller dosages have failed. The antagonistic action of digitalis to the heparin effect may require adjustment of heparin dosage.

We have recently used dicumarol to supplement and supplant heparin because of the large amounts of heparin needed to maintain proper coagulation time. Dicumarol dosage has been as follows: 300 mg. the first day, 200 mg. the second day, and 100 mg. on the succeeding days. By the fourth day the dicumarol may take over for the heparin. Its effectiveness should be checked with daily prothrombin time determinations. The prothrombin time should not be prolonged to the point where spontaneous hemorrhages are likely to occur.

Sympathetic nerve block may be done just before the patient leaves the table. It should be repeated daily. Papaverine should be continued.

*Intermittent Venous Compression.*—Intermittent venous compression may be obtained manually or by mechanical means. In whatever way it is applied, the aim of the therapy is to restrict the venous return from an extremity without obstructing arterial inflow. This will allow an accumulation of blood which will fill the vascular network of the extremity. This is secured by applying a blood pressure cuff and inflating the cuff to a reading of from 50 to 70 mm. of mercury and maintaining that pressure long enough to fill the cutaneous veins. If no veins are visible, the development of a cutaneous flush may be used as indicating a satisfactory filling of the smaller vessels. The pressure may be left off long enough to allow emptying of the vessels. In each case the method and use of intermittent venous compression must be modified. There are mechanical devices which will apply the pressure as long as desired and at as high a pressure as wished.

When the patient is back in bed, intermittent venous compression should be instituted and it should be used continuously. We regard this treatment to be of great importance. In a patient (Case 1) whose sclerotic artery was opened for embolectomy twenty-seven hours after occlusion it was used continuously. He received no heparin, and his leg returned to normal. In another patient (Case 5) the intermittent venous compression was done by hand. The satisfactory appearance of the patient's limb lasted for seven days, with no heparin. At that time treatment was discontinued and by the tenth day the leg was gangrenous.

We have reserved the use of refrigeration for those extremities which were unquestionably beyond therapy, because we feared the possible

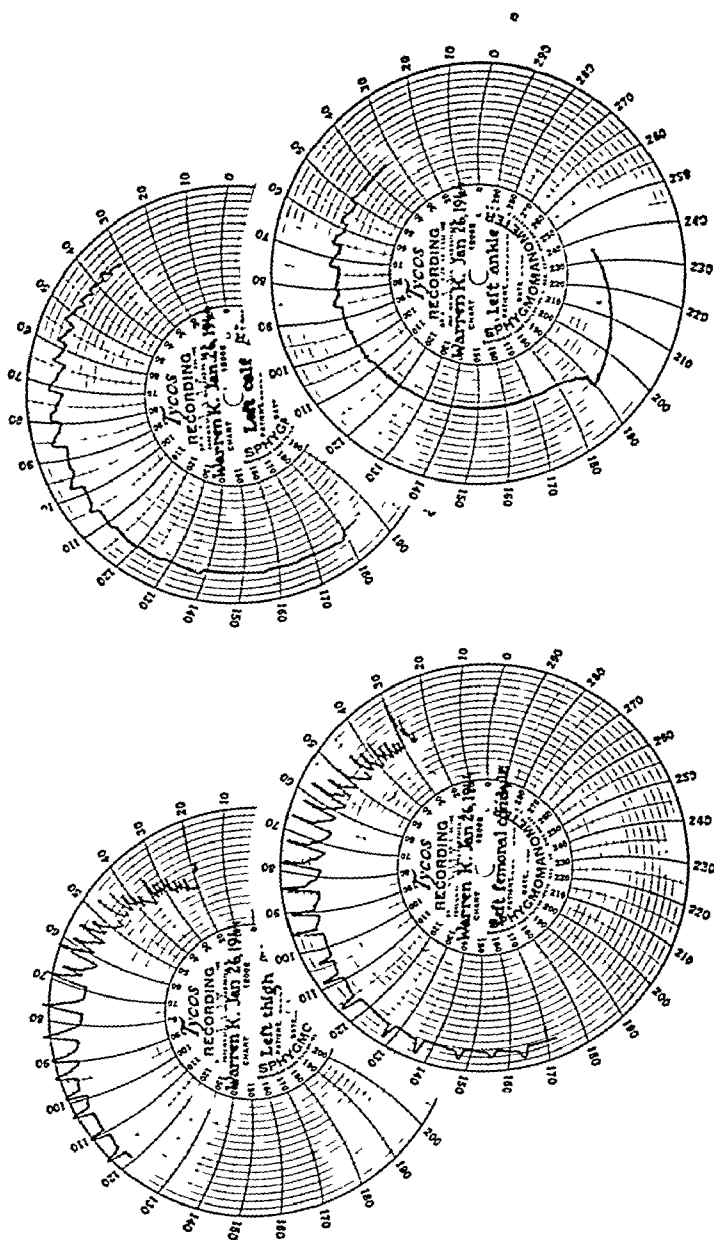


Fig. 11 (Case 2).—Oscillometric tracing taken fifteen months after embolic occlusion of the popliteal artery. Note the definite pulsation in the calf and ankle tracings. These pulses were not present in the immediate period following the lodging of the embolus while the collaterals were taking over.

development of an "immersion limb" as a result of this treatment. Its recent effect on two patients (Cases 12 and 13) has been so encouraging that in the future its use may well be extended.

*Complications.*—Four patients in this series developed significant phlebitis. The first patient (Case 7), who was convalescing after successful removal of an axillary embolus, developed a phlebitis of the left femoral vein which gave rise to a fatal pulmonary embolus. The second patient (Case 15), who was not operated upon for a popliteal embolus, developed a phlebitis three days after the localization of the arterial embolus. A ligation of the superficial femoral vein was done. The third (Case 12) required amputation for gangrene following embolic occlusion of the iliac artery. The common femoral vein was so occluded by thrombosis that a prophylactic ligation was impossible. A fourth patient (Case 5) developed a small pulmonary infarct on the day her leg was amputated but recovered satisfactorily. Prophylactic ligation was not done.

*Duration of Treatment.*—The treatment may be discontinued after a week or ten days when it is apparent that the peripheral pulse has been restored. When this has not occurred or when operation has not been undertaken, the cessation of treatment should be done gradually. The sympathetic block may be dispensed with after a week. Intermittent venous compression may then be given less intensively. The anticoagulant should be continued the longest. Two or three weeks should be a minimum time.

*Analysis of Results.*—The tables presenting our results in the treatment of twenty-four patients with embolic occlusion of major arteries are self-explanatory.

#### DISCUSSION

*Antispasmodics.*—In major occlusions of the lower extremities, Atlas and others<sup>20, 28</sup> have recommended observation of the effect of antispasmodic therapy in the form of papaverine and/or sympathetic block before operation. This recommendation is based upon the possibility that a minor embolus may initiate mass reflex arteriospastic phenomena and that the femoral arteries possibly closed by such spasm may resume pulsation under the influence of the antispasmodics. However, we have not seen such an occurrence. We believe that little harm can be done in exposing a nonpulsating contracted empty femoral artery, whereas the danger of passage of an embolus into the relatively inaccessible periphery is excessive and has occurred in our experience (Cases 9 and 13). In addition, delay adds to the likelihood of thrombosis in the artery peripheral as well as central to the embolus. We agree with those<sup>6, 21, 22</sup> who feel that conservative treatment is to be used only until the patient can be taken to the operating room. Roome's report of failure with sympathetic block emphasizes that it should be used only as an adjunct to other forms of therapy.

TABLE I  
RESULTS TO CIRCULATION IN LIMBS SUBJECTED TO EMBOLECTOMIES

CASE	RESULT
4	Circulation restored—patients died of cardiac disease in less than six days after removal of embolus
5	
6	
10	
16†	
18	
19	Circulation restored permanently but patients died later
20	
1	
2†	
7	
24	
13	Embolus not obtained
9	Embolus moved
11	Result uncertain

\*Two separate emboli removed from different arteries during the same operation.

†Three separate emboli removed at different times—one eight months, one four months, and one six days before death.

The case against the use of antispasmodics has been aptly expressed by Griffiths who says "... if an embolus could be made to move from a critical position, there is no way of guaranteeing that it will move into a safer one." Pratt quotes Lund, McKettrick, and Allen as believing that the arteriospasm prevents the formation of a tail thrombus. However, this opinion is not supported in our experience because in one patient (Case 6) a long tail thrombus was found.

TABLE II  
RELATIONSHIP OF THE TIME INTERVAL BETWEEN DEVELOPMENT OF EMBOLUS AND ITS REMOVAL

(EIGHTEEN ATTEMPTED EMBOLECTOMIES CARRIED OUT ON FIFTEEN PATIENTS;  
FIFTEEN SUCCESSFUL EMBOLECTOMIES OBTAINED IN THIRTEEN PATIENTS)

CASE	TIME INTERVAL (HR.)	RESULT TO LIMB
20	2	Good
18	3	Good
16	4	Good
16	4	Good
2	5	Good
19	5½	Good
2	6	Good
6	6	Good
7	8	Good
5	9	Good (with help)*
4	10	Good
24	18	Good
11	20	Uncertain
10	23	Failure
1	27	Good

\*It will be seen that of the fifteen limbs subjected to embolectomy, ten were operated upon before eight hours; all had satisfactory results. After eight hours the results were variable, but one man (Case 1) recovered when the embolectomy was performed twenty-seven hours after the occlusion.

TABLE III  
RELATIONSHIP OF LOCATION OF EMBOLUS TO RESULTS OF THERAPY

LOCATION	NUMBER OF CASES	RESULTS
Aortic	4	All shifted to lower location
Iliac	8	7 operated upon: 4, immediate restoration of circulation; all died of cardiac disease 1, permanent cure (died of recurrent embolus eight months later) 1, failed to obtain embolus; amputation 1, questionable result; died before circulation definite 1 not subjected to operation; amputation
Femoral	12	10 operated upon: 5, temporary good results 3, permanent good results 2, failures (embolus moved; no restoration of circulation) 2 not operated upon; amputations; 1 died
Popliteal	6	6 not operated upon: 2, amputations 4, recovered
Axillary	2	1 operated upon; recovered 1 not operated upon; recovered

TABLE IV  
RELATIONSHIP OF CARDIAC DISEASE TO EMBOLI AND OUTCOME

NATURE OF CARDIAC LESION	NUMBER OF EMBOLI	DEATHS
Arteriosclerotic (hypertension)	12	4
Rheumatic	5	3
Coronary	2	1
Thyrototoxic myocardial degeneration	1	1
Aortic plaque	1	1
Syphilitic	1	1
Undetermined	2	2

TABLE V  
RESULTS IN PATIENTS WHOSE LIMBS WERE NOT SUBJECTED TO EMBOLECTOMY

CASE	LOCATION OF EMBOLUS	RESULT
3	Popliteal	Recovered
8	Femoral	Amputation
12	Iliac	Amputation
14	Popliteal	Amputation
15	Popliteal	Recovered
17	Popliteal	Recovered
21	Popliteal	Recovered
23	Popliteal	Amputation
22	Axillary	Recovered

NOTE.—Although none of the patients who were not operated upon died, it is seen that most of these occlusions occurred in the more peripheral arteries.

series, only two patients (Cases 5 and 9) died in the immediate post-operative period and in neither was the circulation considered to be adequate. We do not know the significance of this observation.

*General Mortality.*—Although our mortality is high, the mortality is high in other reported series. We do not often see the patients with arm and popliteal emboli because of our known belief that most of these do not require surgical intervention. By excluding this kind of case, our series includes a larger proportion of embolic occlusion of the larger arteries of the lower extremity. This may contribute some to the relatively high mortality in our series.

McClure and Harkins report ten cases, nine involving the lower extremity; one each of popliteal, femoral, and iliac occlusion were treated successfully; two patients of this group died within a year of other emboli. Four successful cases were reported by Lesser without mention of other cases seen or operated upon. Linton reported two successful cases, one of an axillary embolism; two others in which amputation was required, and one successful aortic case treated with intermittent venous compression. He does not state what proportion of his total experience with emboli these reported cases represent. Dickson reported six operations for embolectomy (performed upon five patients). Five of the six limbs required amputation, and one patient recovered. Heparin, intermittent venous compression, and antispasmodics were not employed as a part of the therapy. No mention was made of patients not subjected to operation. In Pearse's six cases published in 1933 heparin was not administered, and intermittent venous compression was not used. Two patients with femoral and popliteal emboli, respectively, required amputation; one with aortic and one with brachial occlusion died, and one with brachial, one with femoral, and one with posterior tibial occlusion were successfully treated. These patients were able to leave the hospital with useful extremities. In Lund's large series of cases an improvement in the rate of survival of limbs was seen on comparing the more recent to the older cases and anticoagulants were not used.

In only two of our own patients (Cases 19 and 24) was the death definitely cardiac, that is, sudden and without warning.

#### SUMMARY

Heparin should be administered as soon as the diagnosis of arterial embolus is made. This is done in order to prevent a thrombosis of the blood distal or central to the embolus, which, should it occur, would make all attempts to restore blood flow futile.

Sympathetic block should not be used in aortic, iliac, or femoral embolic occlusion until the operation has been done, because the resultant vasodilatation may allow the clot to progress and escape into vessels from which it can no longer be removed with ease.

Embolectomy should be done as soon as possible after diagnosis.

Most occlusions of the femoral and iliac arteries and the aorta may be satisfactorily displaced by approach through an incision in the femoral artery.

Emboli in popliteal and axillary vessels require removal only when the use of muscles supplied by the vessels remains impossible.

Heparin, intermittent venous compression, antispasmodics, and/or sympathetic blocks should be used as forms of treatment accessory to embolectomy. They should also be used when no embolectomy is done. Their use must be continued for some time.

Attention must be constantly directed to the cardiac disease which in itself may be fatal.

Twenty-four patients with twenty-seven limbs rendered ischemic by embolic occlusion have been studied. Of these limbs, nine were not operated upon. Eighteen limbs were operated upon. In one patient the embolus had moved, and in a second the embolus could not be obtained. Thus there were sixteen limbs from which an embolus was removed at operation from thirteen patients.

Ten of these emboli were removed within eight hours of their occurrence; all of the patients had satisfactory return of the circulation. Of the remaining six patients, four were successfully treated (one after twenty-seven hours), one result was doubtful and one was a failure.

Twelve of the patients studied died. All of these had had emboli removed. Seven patients died within the first few days after the removal of the embolus, apparently from cardiac failure, and all had had successful restoration of the peripheral circulation. Deaths in four of the remaining five were from causes not related to the heart disease or the embolus and might therefore have been avoided.

#### CASE REPORTS

**CASE 1** (Cook County Hospital).—A. H., a psychotic 60-year-old white male, was suffering from myocardial decompensation at the time he developed an embolic occlusion of the left femoral artery. Although not subjected to embolectomy until twenty-seven hours after the occurrence of the occlusion, and although the artery in which the embolus had lodged was the site of extreme arteriosclerosis, the circulation of the leg recovered sufficiently to allow it to be useful. Heparin was not used, but intermittent venous compression was applied constantly for two weeks. Five weeks after the embolus was removed, and three weeks after all local treatment to his leg was stopped, the patient died from bronchopneumonia.

*Comment.*—At the time of operation no pulse was restored in the periphery of the leg. Intermittent venous compression was used constantly, and it was the impression of all who watched the leg that this treatment was responsible for the recovery of the circulation. Heparin was not used.

**CASE 2.**—M. M., a 53-year-old schoolteacher, entered St. Luke's Hospital Dec. 12, 1941. Three hours previously she had developed pain in both lower extremities and was unable to move either of them. Her previous history mentioned an episode of rheumatic fever in childhood and she had had transient attacks of decompensation which had been treated with digitalis and rest. From December 1 to 4 the patient



took 3 gr. of digitalis daily because of extreme fatigue. On December 4 she developed severe abdominal pain which was treated with morphine; this was followed by numbness and paresthesia in both lower extremities and a transient attack of blindness. On December 7 these symptoms were followed by an embolus in the left femoral artery. When she entered the hospital auricular fibrillation was present. The left leg and foot were immobile, cold, and pulseless. On the right, although no pulse could be felt in the foot, the femoral pulse was easily palpable.

Removal of the embolus from the left iliac artery was done six hours after the onset of symptoms. Retroperitoneal massage was required to obtain the large, soft, red thrombus. Administration of heparin was started four hours postoperatively. Digitalis was discontinued. Postoperatively the femoral and popliteal pulses returned. Those of the foot did not. The circulation of the leg was well restored when the patient left the hospital two weeks after the operation.

Approximately four months later the patient entered the hospital with the same symptoms in the right leg. A similar operation was done on the right leg, four hours after the onset of symptoms. The embolus was found at the level of the origin of the profunda femoris artery. There were pulsations in the dorsalis pedis artery when the patient returned to her bed. Heparin was again used postoperatively as was intermittent venous compression. She was dismissed sixteen days after embolectomy.

A third admission was made July 24, 1942, three months later. A saddle embolus of the aorta was diagnosed three hours after the onset of symptoms. These were not relieved by papaverine. On entrance both femoral arteries were pulseless and both extremities were cold and mottled below the middle of the thigh. Paravertebral block greatly improved the right but not the left side. Left femoral embolectomy was done six hours after onset of symptoms. The embolus was located at and above the previous suture line in the artery. Proximal blood flow was completely restored, but distal flow was poor. Gradual discoloration and intractable pain developed in the left foot and lower leg. On Aug. 6, 1942, an amputation was done below the knee. Some of the muscle looked necrotic. On August 15, nine days after amputation, an embolus occurred in the right femoral artery. The right leg became frankly gangrenous to the upper third of the leg. This right femoral embolus also shut off the remaining circulation to the left leg, and the stump now became gangrenous. Because of elevation of temperature, both legs were packed in ice and an amputation through both thighs was done under refrigeration anesthesia Aug. 27, 1942. The following day the patient developed hyperthermia, convulsions, and loss of consciousness and died. Autopsy confirmed the diagnosis of mitral heart disease and embolus to the bifurcation of the aorta and to the cerebral vessels.

*Comment.*—This patient had had a change of digitalis dosage preceding the development of her first embolic phenomenon. She recovered from two major embolectomies but succumbed when a barrage of emboli progressively blocked her peripheral arteries. The phenomenon of the second embolus on the right, shutting off the remaining source of collateral to both legs, is of interest. The two successful embolectomies were both done within the first six hours of occurrence.

CASE 3 (No. 53795, Cook County Hospital, 1942).—W. K., a white male 30 years of age, suffered from symptoms of cardiac decompensation for two months previous to entrance to the hospital. A cough with occasional blood-tinged sputum was concomitant with anorexia and nausea. At the same time, three weeks prior to entrance to the hospital, he noticed the smoky red color of the urine. At 5 P.M., Oct. 21, 1942, he developed a sudden attack of pain in the left leg. The patient entered the hospital at midnight. At that time he was very ill. Auricular fibrillation was present, pulse was 144, and there were many skipped beats. He was severely decompensated at the time, his liver was palpable below the costal margin, and there were râles audible in both pulmonary bases. The left leg below the knee was cold, white, and

pulseless, but he could still move his toes. Recording oscillographic tracings (Fig. 9) taken at that time show the increased oscillations just above the occlusion and the sudden interruptions of the pulsation at the site of the occlusion. The man was too ill for embolectomy and did not need it since his calf muscles could still be used. The one sympathetic block which was done upset him so that no more were attempted. His leg recovered slowly, the color gradually returned, and he is able to walk on his leg at the present. Although there has been muscle atrophy, he has a very slight foot drop and there is a palpable pulsation in the dorsalis pedis artery which is seen in Fig. 11.

*Comment.*—This patient with rheumatic heart disease was so severely ill that the effort of undergoing lumbar sympathetic block was more than he could tolerate. The usefulness of his calf musculature indicated that a satisfactory outcome might be anticipated. Of particular interest is the return of pulsation in the dorsalis pedis artery after it had been pulseless for days. The use of heparin here might have resulted in a stronger arterial pulse and might have helped assure the patency of the popliteal artery above the embolus.

CASE 4 (No. 41253, St. Luke's Hospital).—G. F., a 42-year-old white female and a known cardiac patient had been taking digitalis irregularly. She had developed symptoms of a saddle embolus at the aortic bifurcation at 4 P.M., but by 7 P.M. the pain had left the right leg which at the same time became warm and pink. When she entered the hospital at 9 P.M. there was no pulse in the left femoral artery. Papaverine and paravertebral block did not relieve the symptoms, and at 2 A.M., March 6, 1943, under general anesthesia, the left iliac artery was exposed through an incision just above the inguinal ligament. The iliac artery was opened and a small embolus removed, and because the clot could not be extracted through this incision, another was made higher in the artery. Through this one the entire massive embolus was extracted. Free massive flow of blood followed. The iliac vein was ligated because the iliac vessel distal to the two incisions was not pulsating vigorously.

The patient was given heparin postoperatively as well as intermittent venous compression and papaverine. Her leg seemed slightly warmer and was pink when the compression was in its positive phase. The leg was painful, however. During the forty-eight hours after the operation her pulse and respiratory rate were elevated and she died from what seemed to be cardiac failure. The clinical impression was that the circulation of her leg had recovered sufficiently to allow it to survive. There were no pulsations in the foot.

*Comment.*—The treatment of this patient might have been improved. First, she should have had heparin preoperatively, but since there was no tail clot seen, this may not have been essential in her case. The iliac might best have been cleared from the femoral artery (see Cases 16, 19, and 20). This would have avoided a general anesthetic.

CASE 5 (No. 12336, Cook County Hospital, 1943).—G. P., a 41-year-old Negro housewife, entered the hospital March 13, 1943, for care of an acute coronary artery occlusion which had developed three days before entrance. While under care the presence of a mild diabetes mellitus was discovered. She was treated for both complaints and did well until April 23, when she developed a sudden pain in the left leg. It could not be moved, and examination revealed pulsation in the femoral artery only as low as a point 5 Cm. distal to the inguinal ligament. A fairly large embolus was removed from the femoral artery nine hours after its occurrence. The embolus had entered the profunda, and this portion of the embolus had to be pulled out to secure retrograde bleeding from the profunda branch. The femoral vein was ligated. No heparin was given postoperatively, but intermittent venous compression was maintained manually by patients on the ward. At the end of a week the leg was warm and had little pain but the foot was cold. The compression at this point was dis-

continued. The leg immediately began to develop blebs and was soon unquestionably lost. An amputation of the thigh became necessary May 12. The stump became infected and the patient succumbed to the infection May 31.

*Comment.*—This patient died from infection of an amputation stump. The amputation might have been avoided if heparin had been available and if an automatic intermittent venous compression could have been maintained for a longer period of time. The sudden change in the condition of the leg following the discontinuance of the intermittent venous compression was striking. Her cardiac condition was not a serious problem in the postoperative course.

CASE 6.—F. H., a 75-year old housewife, had been treated for her cardiac symptoms for about a year. In the period immediately preceding the onset of her embolic phenomenon her digitalis dosage had been increased by 3 gr. daily. On April 11, 1943, at about 3 p.m. she developed agonizing pain in the left leg. She was brought to St. Mary's Hospital in Streator, Ill., by her physician, April 12, and at that time gave the history that at 6 a.m. she had developed similar pain in the right leg. The left leg at that time was severely discolored halfway to the knee, but the right leg was merely of marble whiteness (Fig. 5). The right leg was operated upon at 10 a.m. and an embolus was removed from the femoral artery at a point about 6 cm. distal to the inguinal ligament four hours after it had lodged there. Attached to this embolus was a tail thrombus twenty-six inches long (Fig. 2). The condition of the leg immediately after operation was very satisfactory, and although there were no palpable pulses, the leg was warm and the pain gone. Intermittent venous compression was applied to both limbs. The patient's cardiac condition, grave since the onset of the embolic phenomena, increased in severity and she died thirty-six hours after the operation.

*Comment.*—In this instance the successful early removal of the arterial obstruction resulted in satisfactory circulation to the involved extremity. The patient succumbed in the immediate postoperative period to her cardiac disease. The relationship of the digitalis therapy to the development of the emboli in this case is not precise since the exact date of change of digitalis therapy is not known.

CASE 7 (No. 21705, Cook County Hospital).—E. J., a white male 46 years of age, entered the hospital for care of a bleeding gastric ulcer May 5, 1943. On the sixth day of hospital stay he developed a cold, painful arm. The forearm was useless. Although no source for an embolus could be predicated from his complaints or examination, such a diagnosis was made of necessity. A clot one and one-half inches long was removed from the distal portion of the axillary artery, and the clot extended down into the circumflex humoral artery. Embolectomy was done less than twelve hours after onset of symptoms. The arterial pulsation did not return in the arm, but there was immediate improvement in the color of the hand, which could now be used. Intermittent venous compression was started. A stellate ganglion block was done at the conclusion of the operation and was repeated daily. Too much compression led to a slight edema of the hand which was corrected when the pressure was readjusted. The patient's hand was out of danger within a week after the embolectomy. He continued to bleed from his gastric lesion, for which transfusions were given. He developed recurrent attacks of thoracic pain which were finally recognized as due to pulmonary infarcts arising from an obscure thrombosis of the deep calf veins of the left leg. Frank femoral thrombosis finally developed and a massive fatal pulmonary embolus occurred June 16, 1943. His arm was in good condition at that time. Autopsy reported the following findings: Acute empyema of the left pleura after subacute embolus in the main branch of the pulmonary artery of the left lower lobe, following old thrombosis of the left femoral vein; multiple recent anemic infarcts of the right lower lobe after emboli; compression atelectasis of the left lung; compensatory emphysema of the right lung; moderate sclerosis of the ascending aorta with a shallow ulcer at the crest of the

arch and a large mural thrombus; scar in the left axilla after removal of thrombus in the brachial artery; severe parenchymatous degeneration of the myocardium with moderate coronary sclerosis; progressive circular carcinoma of the pylorus with acute marginal bleeding ulcers; progressive nephrosclerosis; chronic ulcerative proctitis.

*Comment.*—This patient developed the arterial embolus from the mural thrombus of the arch of the aorta. Although the upper extremity is rarely seriously endangered by emboli lodged in the arteries, this was thought to be an operative case because the obstruction was sufficient to render the forearm useless. The pulmonary embolus might have been prevented by prophylactic femoral vein ligation. The carcinoma of the stomach was resectable. Aside from the mural ulceration of the arch of the aorta, his serious maladies were amenable to therapy.

CASE 8 (No. 32807, Cook County Hospital, 1943).—F.S., a white male 40 years of age, was being treated for coronary artery occlusion. At 2 P.M., July 23, 1943, eleven days after coronary artery occlusion, he developed a pain in the left leg as high as the knee. The left leg was mottled, cold, and pulseless, and the patient was unable to move the toes voluntarily. Nitroglycerine was given at that time. The patient was seen at 11 A.M. the next day, twenty-one hours after the occlusion. The cessation of arterial pulsation in the left femoral artery was palpable just 3 cm. distal to the inguinal ligament. The leg was cold and pulseless, and the patient could not move the toes voluntarily. While being examined there was a sudden change of the color of the leg. It seemed to develop some circulation and the distinct line which seemed to separate the mottled area of the leg from the normal area became less sharply demarcated. Thinking that this indicated either a shift of position of the embolus or the widening of significant numbers of collateral vessels, it was noted that the venous filling time was but little prolonged. Nonoperative treatment was decided upon. Heparin was administered, intermittent venous compression instituted, and paravertebral sympathetic blocks were given daily. By July 30 there was definite mottling over the entire calf but no blisters were visible. At that time it was not thought that the leg was unquestionably lost. By August 3 blebs had formed and on August 5 the leg was amputated because of severe pain. The patient is alive and walking on crutches today.

*Comment.*—This patient developed a peripheral embolus eleven days after his myocardial infarction. His case is of particular interest because of the apparent spontaneous improvement in the circulation which occurred twenty-one hours after the embolus developed. This change in circulation was not sufficient to maintain the viability of the leg, which subsequently required amputation. However, in this instance the leg was not unquestionably lost for over a week, and it was the feeling of physicians who watched the patient's progress that the heparin, intermittent venous compression, and paravertebral sympathetic blocks would have been successful had an embolectomy been done, even as late as twenty-one hours when the change in circulation took place.

CASE 9 (No. 40404, 1943).—E.W., an elderly Negro female, entered the hospital Aug. 31, 1943. Her condition was diagnosed as an acute cholecystitis with perforation and possible subdiaphragmatic abscess. On the twenty-fifth day of her stay she developed a sudden attack of pain in the left foot. The leg was cold and pulseless and she was unable to move the toes two hours after the onset. Twenty-two hours after the onset a definite and abrupt cessation of palpable pulsations in the femoral artery was palpable 3 cm. distal to the inguinal ligament. She had been given papaverine and one lumbar sympathetic block. An embolectomy was advised and a spinal anesthetic instituted. When the patient's thigh was palpated, the spot of arrest of femoral pulsations was no longer palpable. An incision was made over the femoral artery which was found to be patent and pulsating. It seemed that the spinal anesthetic had allowed the embolus to pass farther down the artery. No

oscillometer was available at the time. The leg progressed to develop gangrene. This served to exclude a diagnosis of arterial spasm. The condition of the patient became progressively worse and she died Oct. 9, 1943, thirty-nine days after entry and thirteen days after the embolic episode.

*Comment.*—The important observation in this patient is the shift of position of the embolus which occurred after the spinal block. That it was not simply an arterial spasm is proved by the development of gangrene in the leg. The gall bladder condition was amenable to therapy and had the embolus been easily recovered from the femoral artery, the patient's clinical course might have been improved.

CASE 10 (No. 44128, Cook County Hospital, 1943).—A. S., a 49-year-old white woman, had known of her hypertension for five years. She entered the hospital Sept. 27, 1943, stating that at 1 P.M. she had developed numbness and pain in the right toes and leg. A transient attack in the left hand had occurred three days previously. When she was examined she was seen to be acutely ill, the blood pressure was 160/110, her pulse rate was 140, and she was cyanotic. The right leg was pale, cold, and useless. The point of arrest of the pulsations in the femoral artery was easily palpated 3 cm. below the inguinal ligament. The embolus was presumed to arise from the heart, diseased from her hypertension. At 10:30 A.M., September 28, a femoral embolectomy was done, twenty-one and one-half hours after the development of the embolus. There was marked adherence of the embolus to the surrounding arterial wall. Satisfactory circulation to the periphery was not re-established. The posterior tibial artery was exposed and an attempt was made to pass a ureteral catheter up the posterior tibial artery, but it was impossible to obtain through-and-through circulation of saline solution in this way. The femoral vein was tied.

The leg continued to discolor and an amputation was done October 11. A subsequent electrocardiogram was read as follows: Advanced left ventricular preponderance with rather marked ischemia of the anterior coronary branch but no evidence of coronary occlusion or infarction.

*Comment.*—The obvious difficulty here was the late operation and the lack of heparin in the pre- and postoperative treatment. The attempt to obtain retrograde clearance of the arterial network by forceful irrigation of the posterior tibial artery was unsuccessful. It might have been useful if the peripheral thrombosis had not progressed so far.

CASE 11 (No. 53428, Cook County Hospital, 1943).—L. L., a very obese 73-year-old white female, entered the hospital Dec. 2, 1943, suffering from myocardial decompensation with auricular fibrillation, best explained as due to cardiac hypertrophy concomitant to hypertension. She was treated with digitalis, 3 gr. being given daily. She improved surprisingly, so that by December 7 the pulse was 64. By the morning of December 8 she noted pain in the left leg, the onset of which was indefinite, because the patient was somewhat disoriented and did not answer questions accurately. The leg was cold and totally pulseless and she could not move it. A diagnosis of iliac embolus was made and an embolectomy was decided upon. At 8 P.M. the embolus was removed from the iliac artery just above the inguinal ligament. The femoral vein was ligated. Postoperatively she did not do well, was very restless, and it was impossible to maintain either proper heparin therapy (although some was given) or intermittent venous compression. Her cardiac condition remained very poor and she died December 13, five days after removal of the embolus. It was uncertain at that time whether or not the leg would have survived.

*Comment.*—The long delay in therapy occasioned by the patient's cerebral condition was important here. The failure to give heparin preoperatively may have had a bearing on the condition of the leg. Whether or not her restlessness, which prevented intermittent venous compression, was sufficient to encourage the movement of blood in the extremity may be speculated.

CASE 12.—(St. Luke's Hospital).—M. G., a septagenarian woman, was brought to the hospital Jan. 11, 1944, because of a transient hemiplegia which had developed in the course of a cardiac disturbance. She had had hypertension for several years. When she entered the hospital, the diagnosis of auricular fibrillation complicating the cardiac changes of hypertension was made. This was corroborated by the electrocardiogram which pointed to a coronary artery disease which could have been the result of multiple myocardial infarctions. During her stay in the hospital she was irrational. On January 17 it was noted that there was marked discoloration below the lower third of the calf. The leg was warm as low as the knee, but there was no pulsation palpable in the femoral artery. Irreversible changes had already occurred in the leg. The leg was kept cold, during which time the cardiac condition improved, and January 25 a supracondylar amputation was done, using refrigeration as the means of anesthesia. The patient is still in the hospital, the cardiac and cerebral conditions requiring the hospital stay.

*Comment.*—The femoral artery was one of many arteries occluded when this patient developed a cardiac crisis. The cerebral embolus no doubt gave rise to the psychic changes which prevented the patient from complaining when the iliac artery was occluded. The rapidity with which the peripheral changes became irreversible may be explained as due to the circulatory inefficiency and may well have been prevented by early administration of heparin.

CASE 13 (No. 57121, Cook County Hospital, 1943).—M. M., a 34-year-old white female entered the hospital Dec. 28, 1943, suffering from severe auricular fibrillation. The basis of this was rheumatic heart disease. She had taken digitalis irregularly since she had developed myocardial decompensation two and one-half years before. A severe cold had preceded the present attack. When she was examined her pulse was 140 per minute and was very irregular, and there was evidence of decompensation in that there were râles in both pulmonary bases and in that the liver was palpable three inches below the costal margin. She was given  $1\frac{1}{2}$  gr. of digitalis four times daily. On December 30 her pulse was 100. On December 31 the digitalis was reduced to  $1\frac{1}{2}$  gr. twice each day. Fibrillation was still present. On Jan. 1, 1944, the dosage of digitalis was cut to  $1\frac{1}{2}$  gr. every morning. The lungs were clear. On January 4 there was great pain in the right renal region and a diagnosis of right renal infarct was made. On January 13 her pulse was 60 at the apex and 55 at the wrist. Digitalis was stopped. She was apparently ready to get up. At 4:40 P.M. she developed paresthesias of both legs. There were no pulsations in either leg. A diagnosis of saddle embolus at the aortic bifurcation was made. By 6:40 P.M. pulsations were found in the left femoral artery and it was presumed that the embolus had been washed into the right iliac vessels. At 8:30 P.M. 5 c.c. of heparin were given and at 9:25 P.M. operation was begun. We were unable to extract the embolus from where it had apparently lodged at the bifurcation of the iliac vessels. Spasm of the iliac artery was so great that at times it grasped the probe. We hoped that the spasm was the entire cause of the ischemic extremity. The gangrene which developed after the operation was evidence that there was a definite organic occlusion. The gangrene developed in spite of the use of heparin, paravertebral blocks, and ice bags applied to the leg. Since then the patient has had a major embolic occlusion of the left leg, which required amputation, and has had recurrent episodes of emboli to the upper extremities and to the cerebral circulation.

*Comment.*—The failure to remove the embolus in this patient was due to the reluctance to introduce the knobby instrument above the level of the occlusion and actively to extract the embolus which had no doubt been tightly wedged into the internal iliac artery. Experiences with three other patients (Cases 16, 19, and 20) in whom similar situations were encountered lead us to feel that such a difficulty would not remain unsolved in the future. The continued use of heparin was under-

oscillometer was available at the time. The leg progressed to develop gangrene. This served to exclude a diagnosis of arterial spasm. The condition of the patient became progressively worse and she died Oct. 9, 1943, thirty-nine days after entry and thirteen days after the embolic episode.

*Comment.*—The important observation in this patient is the shift of position of the embolus which occurred after the spinal block. That it was not simply an arterial spasm is proved by the development of gangrene in the leg. The gall bladder condition was amenable to therapy and had the embolus been easily recovered from the femoral artery, the patient's clinical course might have been improved.

CASE 10 (No. 44128, Cook County Hospital, 1943).—A. S., a 49-year-old white woman, had known of her hypertension for five years. She entered the hospital Sept. 27, 1943, stating that at 1 P.M. she had developed numbness and pain in the right toes and leg. A transient attack in the left hand had occurred three days previously. When she was examined she was seen to be acutely ill, the blood pressure was 160/110, her pulse rate was 140, and she was cyanotic. The right leg was pale, cold, and useless. The point of arrest of the pulsations in the femoral artery was easily palpated 3 cm. below the inguinal ligament. The embolus was presumed to arise from the heart, diseased from her hypertension. At 10:30 A.M., September 28, a femoral embolectomy was done, twenty-one and one-half hours after the development of the embolus. There was marked adherence of the embolus to the surrounding arterial wall. Satisfactory circulation to the periphery was not re-established. The posterior tibial artery was exposed and an attempt was made to pass a ureteral catheter up the posterior tibial artery, but it was impossible to obtain through-and-through circulation of saline solution in this way. The femoral vein was tied.

The leg continued to discolor and an amputation was done October 11. A subsequent electrocardiogram was read as follows: Advanced left ventricular preponderance with rather marked ischemia of the anterior coronary branch but no evidence of coronary occlusion or infarction.

*Comment.*—The obvious difficulty here was the late operation and the lack of heparin in the pre- and postoperative treatment. The attempt to obtain retrograde clearance of the arterial network by forceful irrigation of the posterior tibial artery was unsuccessful. It might have been useful if the peripheral thrombosis had not progressed so far.

CASE 11 (No. 53428, Cook County Hospital, 1943).—L. L., a very obese 73-year-old white female, entered the hospital Dec. 2, 1943, suffering from myocardial decompensation with auricular fibrillation, best explained as due to cardiac hypertrophy concomitant to hypertension. She was treated with digitalis, 3 gr. being given daily. She improved surprisingly, so that by December 7 the pulse was 64. By the morning of December 8 she noted pain in the left leg, the onset of which was indefinite, because the patient was somewhat disoriented and did not answer questions accurately. The leg was cold and totally pulseless and she could not move it. A diagnosis of iliac embolus was made and an embolectomy was decided upon. At 8 P.M. the embolus was removed from the iliac artery just above the inguinal ligament. The femoral vein was ligated. Postoperatively she did not do well, was very restless, and it was impossible to maintain either proper heparin therapy (although some was given) or intermittent venous compression. Her cardiac condition remained very poor and she died December 13, five days after removal of the embolus. It was uncertain at that time whether or not the leg would have survived.

*Comment.*—The long delay in therapy occasioned by the patient's cerebral condition was important here. The failure to give heparin preoperatively may have had a bearing on the condition of the leg. Whether or not her restlessness, which prevented intermittent venous compression, was sufficient to encourage the movement of blood in the extremity may be speculated.

heavy household duties particularly exhausting. In the period immediately preceding her entry into the hospital she had had a moderate amount of hemoptysis. She entered the hospital Jan. 31, 1944, with myocardial decompensation. She was given 3 gr. of digitalis on entrance and  $1\frac{1}{2}$  gr. every morning thereafter. On Feb. 6, 1944, at 1 P.M. the patient noted a sudden onset of tingling, followed by a sensation of cold in both lower extremities. After about ten minutes the legs became unbearably painful and she noted that she could not move either leg. At that time it was thought that she had developed a saddle embolus at the aortic bifurcation. A paravertebral block was done on both sides. After this the right femoral artery was palpable, pulsating to a point  $\frac{1}{2}$  cm. below the inguinal ligament, at which point it abruptly stopped. There was no palpable pulsation on the left side. The patient was given 5 c.c. of heparin and taken to the operating room at 5 P.M. Both femoral arteries were exposed in the inguinal region. The left femoral artery was opened first; it was empty, and an enormous folded clot (Fig. 1) was extracted from above where it apparently had lodged at the point of bifurcation of the iliac vessels. Free pulsation attested to the return of circulation, and the arterial incision was closed. The right femoral artery was opened at the site of occlusion, the point of femoral bifurcation, and the clot was removed (Fig. 1). The left femoral vein was ligated.

The patient's postoperative course was marked by a totally satisfactory circulation in both legs, which were warm, useful, and free of pain. The cardiac condition increased in gravity and she died thirty-two hours after operation in the picture of an acute cardiac failure.

*Comment.*—The early removal of the emboli from the occluded vessels in this patient was associated with the administration of heparin preoperatively. The successful result was followed by serious cardiac failure. Of particular interest was the precipitation of the cardiac attack by undue fatigue. In this patient the iliac embolus was extracted by making sure that the knobby end of the probe was above the embolus. The probe was then turned laterally and pulled down. This maneuver, not done in Case 13, might have been successful there. The heparinized blood did not coagulate in the operating room, but both arteriotomy wounds stopped bleeding without difficulty.

CASE 17 (No. 7634, Cook County Hospital, 1944).—J. M., a 60-year-old white male, was admitted to the hospital for care of myocardial decompensation. While being examined he experienced a sudden pain in the left leg. The pain was severe and constant, and numbness soon was noted. The toes were constantly useful. At that time the popliteal and femoral pulses were palpable, but neither dorsalis pedis nor posterior tibial pulse could be made out. A diagnosis of embolic occlusion of the bifurcation of the popliteal artery was made, but since the toes could be moved, it was felt that there was sufficient collateral to allow the patient to be treated without operative intervention. Papaverine was given and the patient recovered sufficiently to have good pulses in both posterior tibial and dorsalis pedis arteries.

*Comment.*—This patient was correctly treated without embolectomy because the usefulness of the calf muscles indicated adequate collateral. The return of good pulsation in the dorsalis pedis and the posterior tibial makes one feel that there may have been a good deal of arterial spasm involved in this clinical picture. It is difficult to conceive how an embolus large enough to have blocked the popliteal could so pass into a collateral large enough to hold it and still leave the anterior and posterior tibial vessels open. The patient did not develop cephalad thrombosis as did the one reported in Case 14. Heparin would have rendered such an occurrence unlikely.

CASE 18 (No. 8079, Cook County Hospital, 1944).—A. S., a 60-year-old white female, entered the hospital February 24. For eight months previously she had had complaints of dyspnea and swelling of her ankles; hemoptysis had occurred during the first seven days. A sense of oppression over the heart was present. On examina-



taken to maintain the fluid state of the blood and to make use of every possible opportunity for adequate circulation to develop about the obstructed arterial segment. The use of the ice bag seemed to prolong the life of the limb and allowed a lower amputation than would have been possible otherwise.

CASE 14 (No. 1552, Cook County Hospital, 1944).—M. B., a 67-year-old Negro female, had a previous record in the hospital as a cardiac patient. She had had recurrent attacks of cardiac decompensation. Her last hospital stay had been in November, 1943. She entered the hospital Jan. 11, 1944, with similar complaints and findings; her pulse rate was 130 per minute and her blood pressure, 200/110. The diagnosis of myocardial decompensation was again made; she was given digifolin, 3 gr. three times the first day, and  $1\frac{1}{2}$  gr. twice daily thereafter. By January 15 her pulse was 78 and the digitalis was slowed to  $1\frac{1}{2}$  gr. every morning. On January 17 she had developed anorexia and a bigeminal pulse. This was interpreted as a sign of digitalis toxicity and the drug was discontinued. At 7:30 that evening she developed severe pain in the right leg. The leg was cold, but she could move the toes. There was neither dorsalis pedis or posterior tibial pulse. An occlusion of the popliteal artery was suspected, but since pulsations of the popliteal artery were palpable, the occlusion was presumed to be at its lowermost portion, where the bifurcation occurred. Paravertebral blocks were given daily, but on January 20 the foot was obviously discolored. At this time palpation of the popliteal fossa revealed that the pulsations which previously had been easily palpable had disappeared. An amputation was necessary on January 27.

*Comment.*—The development of thrombosis central to the position of occlusion in this patient is a point of great importance. It is probable that the use of heparin soon after the embolus has lodged would prevent thrombosis in patients with such an involvement as this who are not operated upon, as well as in those in whom operation is performed. This emphasizes the importance of anticoagulants in the treatment of embolic occlusion, whether or not operative removal of the embolus is undertaken. Intermittent venous compression might have been of help here.

CASE 15 (No. 3281, Cook County Hospital, 1944).—I. G., a 79-year-old white woman, entered the hospital for treatment of diarrhea. It was discovered that she was suffering from a rapid auricular fibrillation. The fundamental cardiac disease was presumed to be hypertension, even though her blood pressure on entrance was only 140/100. On January 28, six days after entrance, her fibrillation had disappeared. At 11 A.M. the patient developed pain in the left leg but said nothing about it. By 2:30 P.M. the dorsalis pedis was noted to be absent. At 3:50 P.M. she was unable to move her calf muscles. The venous filling time in that leg was one minute and twenty seconds as compared to twenty seconds in the good leg. The popliteal artery pulsed at least throughout two thirds of its length. An embolectomy was decided upon. No heparin was available for preoperative treatment. On the way to the operating room she experienced a marked relief of pain in her leg and a sense of warmth returned. When examined, her leg was warm and there was no return of palpable pulse in the dorsalis pedis and popliteal arteries, but she could move the toes with ease. It was obvious that her circulation had been adequately restored. Her convalescence was uneventful. No operation was performed.

*Comment.*—A small embolus which blocked the bifurcation of the popliteal seriously apparently became fragmented and passed into the peripheral vessels. This allowed the establishment of enough collateral to render operative intervention unnecessary. Probably heparin should be given prophylactically to such a patient (see Case 14).

CASE 16 (No. 4487, Cook County Hospital, 1943).—E. D., a white woman 38 years of age, had known of her cardiac condition since childhood. This cardiac condition had given her considerable difficulty with each pregnancy. It had made her

present and probably resulted from the changes in the myocardium resultant from long-standing hyperthyroidism. She developed a painful leg with resultant loss of movement Feb. 26, 1944, but this disappeared rapidly. On March 1, at 3 P.M. the intern had visited her and specifically noted that she could move her left toes. At 4:25 P.M. she complained of inability to move the left toes and of pain in the entire leg. At that time no pulse could be palpated in the left leg. Ten cubic centimeters of heparin were given at 5:30 P.M. and the femoral artery opened about two hours after the embolus lodged. There was a moderately long tail thrombus found at the site of incision (Fig. 3), and a large clot was removed from the level of the bifurcation of the iliac vessels by the use of a long, lead ball stone-probe. Bleeding was free. The heparin was continued postoperatively, and the patient's leg did well post-operatively; by the end of twenty-four hours she was able to use the muscles in the calf. She died poorly from the cardiac point of view and died forty-eight hours after the embolectomy from her cardiac condition.

*Comment.*—The careful observations of the house officer allowed a correct diagnosis of iliac embolism to be made in the face of a difficult clinical history. The early removal of the embolus associated with the use of heparin resulted in a successful restoration of circulation to the femoral vessels. In spite of the early diagnosis and the use of heparin, some tail thrombus had already formed. It is presumed that without heparin an even larger thrombus would have formed and rendered all attempts at restoration of circulation futile.

CASE 21 (No. 10234, Cook County Hospital, 1944).—P.O., a 63-year-old white male, was under treatment for cardiac decompensation and was progressing satisfactorily until the morning of March 10, 1944, when he found he could not stand on his right leg. The leg was cold and he was not able to move the toes of the foot as well as those of the left foot. He was able to move them, however. Because of the pain in the foot, the pulseless foot, the presumption was that the occlusion had occurred in the popliteal artery. The fact that he was able to use his toes made operative intervention seem unnecessary. Paravertebral blocks and papaverine resulted in a rapid return of warmth to the leg, and by the end of a week the leg was useful. Pulses did not return to the dorsalis pedis or posterior tibial arteries.

*Comment.*—This patient developed an embolic occlusion distal to the main portion of the popliteal artery. The maintenance of peripheral circulation resulted in the retention of ability to move the toes. Heparin would have added certainty to the favorable outcome.

CASE 22 (No. 12442, Cook County Hospital, 1944).—F.C., a 61-year-old white male, entered the hospital March 26, 1944, complaining of pain in the right arm and hand of a dull nature. He stated that his fingers felt numb and that he could move them with difficulty. He had been given  $1\frac{1}{2}$  gr. of digitalis because of ankle edema. His pulse was 70 and fibrillating; blood pressure, 190/90. He could move the fingers easily. Palpation of the axillary artery was easy, and the point of arrest of pulsation was readily felt at about the level of the insertion of the pectoralis major muscle into the humerus. The embolus could be palpated, distending the artery. No pulses were palpable in the periphery. A block of the stellate ganglion was done; he felt an improvement of the temperature of his fingers and he was able to move them better. This was continued daily and his arm recovered.

*Comment.*—This patient who developed an easily diagnosed embolism to the axillary artery had sufficient collateral to allow use of the musculature of the forearm. Hence embolectomy was unnecessary and he had progressed satisfactorily. Heparin would add assurance against cephalad thrombosis.

CASE 23.—Mrs. J., in her middle fifties, known to have hypertensive heart disease, complained of pain, numbness, and a sense of cold in her right leg below the knee. These symptoms had been present for twenty-four hours when she was first

tion the pulse was 120, and the blood pressure was 190/40 in both arms. Her left pupil was larger than the right; both reacted to light and accommodation. A diagnosis was made of syphilitic disease of the central nervous system and of the heart. The latter had produced an aortic regurgitation and the patient was now suffering from myocardial decompensation. She was given  $1\frac{1}{2}$  gr. of digifolin, and by Feb. 29, 1944, she had received 24 gr. in four days. Her pulse had dropped from 120 to 88 per minute. A transient fibrillation had disappeared. At 5 P.M. the patient had a sudden attack of pain in the left leg, which became white, and she was unable to move the muscles of the calf. Palpation revealed a sudden cessation of femoral pulsation 5 cm. below the inguinal ligament. A diagnosis of embolic occlusion of the femoral artery at the level of bifurcation was made. Five cubic centimeters of heparin were given intravenously at 7:15 P.M. and she was given papaverine. Oxygen was given and three hours after the embolus lodged in the femoral artery, it was removed through an incision in the superficial femoral. The patient's vessels were noted to be as soft and pliable as those of a young adult. The patient's leg was warm and pink at the conclusion of the operation, and there was a very strong pulse in both the dorsalis pedis and in the posterior tibial arteries. All the pain disappeared from the leg before the patient left the operating room. The patient was maintained on heparin for six days and was given 300 mg. of dicumarol on the day of the operation and 200 mg. on the remaining days. Her leg remained in perfect condition, but her cardiac condition, after having improved during the first three postoperative days, became worse and she died on the sixth day.

*Comment.*—The total relief of the arterial obstruction in this patient resulted from the fortuitous combination of early administration of heparin plus early embolectomy. The unfortunate fatal outcome might have been anticipated since it is rare for a syphilitic cardiac lesion to give rise to emboli. There was, however, a definite period of auricular fibrillation noted.

CASE 19 (No. 8661, Cook County Hospital, 1944).—T. A., a 52-year-old white man, entered the hospital Feb. 28, 1944. At that time he was suffering from myocardial decompensation and diabetes mellitus. The cause of the cardiac decompensation was not known. He was given supportive treatment and digitalis, 3 gr. daily. On March 1, 1944, after having received only 9 gr. of digitalis, the patient developed an embolus to the left iliac vessels. The leg was cold, pulseless, white, and useless. Ten cubic centimeters of heparin were given intravenously four hours after the occurrence of the embolus, and the embolus was removed five and one-half hours after its occurrence, one and one-half hours after the heparin had been given. At the time of operation there was a tail thrombus three and one-half inches long extending into the femoral vessel (Fig. 4). The clot itself had to be forcefully pulled out of the iliac by engaging it with the scoop end of a lead bile duct probe. The flow of blood was violent as soon as the clot was removed. The femoral vein was not ligated. Postoperatively heparin therapy was continued, as was the papaverine. Dicumarol, 300 mg., was given. The patient's leg felt much better immediately postoperatively but there was no pulse. The next morning his leg and foot were warm and he could move his toes. At noon, just twenty-four hours after the removal of the femoral embolus, just after he had asked for dinner, he died suddenly.

*Comment.*—The death of the patient was obviously of cardiac origin. The leg had made a satisfactory recovery from its temporary occlusion. The rather massive tail thrombus which was present shows clearly the importance of administration of heparin. It is possible that if heparin had been given earlier, it might not have formed; that if the heparin had not been given, the entire arterial network would have been filled with clot.

CASE 20 (No. 7546, Cook County Hospital, 1944).—F. K., a 67-year-old white female, was being treated for hemiplegia which apparently had resulted from a cerebral arterial embolism. Auricular fibrillation and myocardial decompensation were

Since there was no pallor of the extremity and since at the time of operation the distal superficial femoral seemed totally patent, no antispasmodics aside from papaverine were used.

The patient died suddenly during the night two and one-half weeks after the embolectomy. The preceding day he had had full use of his leg, and all therapy had been discontinued.

*Comment.*—The successful outcome of this patient's limb may be attributed to a combination of factors in addition to the underlying cardiac care. There was a fairly good collateral circulation during the time the embolus was lodged in the femoral artery, heparin was used preoperatively, the embolus was removed easily, and the postoperative care combined anticoagulants, intermittent venous compression, and antispasmodics.

It is of interest to point out that the patient had a temperature of over 102° F. postoperatively which required three days to disappear. This temperature may have represented absorption of toxic material which resulted from the inadequate blood supply to the periphery.

The authors wish to acknowledge the cooperation of the Attending Staff of the Cook County Hospital in allowing them the courtesy of seeing the patients in this series who were in the Cook County Hospital.

The authors wish to take this opportunity of expressing their gratitude to the House Staff at the Cook County Hospital for their help in controlling the heparin therapy.

#### REFERENCES

1. Atlas, Lawrence N.: The Management of Acute Embolic Occlusion of the Arteries of the Extremities, *Surg., Gynec. & Obst.* 74: 236-239, 1942.
2. Crafoord, C.: Heparin as a Prophylactic Against Postoperative Thrombosis, *Acta med. Scandinav.* 107: 116-121, 1941.
3. Danzis, Max: Arterial Embolectomy, *Ann. Surg.* 98: 249-272, 422-437, 1933.
4. Dickinson, Arthur M.: Embolism of the Peripheral Arteries, *Am. J. Surg.* 57: 508-512, 1942.
5. Griffiths, D. Le.: Arterial Embolus, *Lancet* 2: 1339, 1938.
6. Heanley, Lawrence: Arterial Embolectomy, *Lancet* 1: 696, 1939.
7. Herrmann, George R., Willis, J. S., McKinley, W. Frank, and Karotkin, Lester: Embolus and Secondary Thrombosis of the Bifurcation of the Aorta, *Am. Heart J.* 26: 180, 1943.
8. Jorpes, Eric: Pure Heparin for the Prevention and Treatment of Thrombosis, *Acta med. Scandinav.* 107: 107-115, 1941.
9. Key, Einar: Embolectomy on the Vessels of the Extremities, *Brit. J. Surg.* 24: 350-361, 1936.
10. Lewis, Thomas: Pain as an Early Symptom of Arterial Embolism and Its Causation, *Clin. Sc.* 2: 237-251, 1936.
11. Lindgren, Stig, and Wilander, Olof: The Use of Heparin in Vascular Surgery, *Acta med. Scandinav.* 107: 148-160, 1941.
12. Linton, Robert R.: Peripheral Arterial Embolism, *New England J. Med.* 224: 189, 1941.
13. Lund, McKettrick, and Allen: Quoted by Pratt,<sup>22, 23</sup>
14. Lund, Charles C.: Treatment of Embolism of the Greater Arteries, *Ann. Surg.* 100: 880-909, 1937.
15. MacFarlane, J. A.: Multiple Emboli Treated Surgically, *Brit. M. J.* 1: 971, 1940.
16. McClure, Roy D., and Harkins, Henry N.: Recent Advances in the Treatment of Peripheral Arterial Embolism, *SURGERY* 14: 747, 1943.
17. Murray, D. W. Gordon: Embolism of Peripheral Arteries, *Canad. M. A. J.* 35: 61-66, 1936.
18. Murray, D. W. Gordon: Aortic Embolectomy, *Surg., Gynec. & Obst.* 77: 157-162, 1943.
19. Murray, D. W. Gordon, and Best, Charles H.: Use of Heparin in Thrombosis, *Ann. Surg.* 108: 163-177, 1938.
20. Neuhoft, Harold: Embolectomy With Partial Arterial Occlusion for Embolism of the Extremities, *Ann. Surg.* 96: 44, 1932.

seen by her physician March 22, 1944. At that time her pulse rate was 140 and irregular and there was some pulse deficit. Examination of the right leg revealed the palpable pulse in the popliteal fossa but none in the foot. Her foot was cold but she could move the toes. Diagnosis was made of hypertensive heart disease with auricular fibrillation and embolus to the right popliteal artery. Cardiac care was given in the home. When seen by one of us (J. T. R.) two weeks later her condition was much the same. Being influenced by the events which occurred in another of our patients (Case 14), anticoagulants were suggested at this time but were not obtainable. By the time two more weeks had passed by, her toes had all become gangrenous and there was a possibility that a portion of the foot would be lost. The cardiac condition had improved markedly.

*Comment.*—This case followed the course of events which occurred in Case 14. Anticoagulants and intermittent venous compression, as well as antispasmodics, might have maintained the viability of the leg long enough for adequate collateral to develop. It is probable that if they had been vigorously applied even at the end of two weeks the slowly developing gangrene might have been prevented.

CASE 24.—Mr. V. I., 72 years of age, was admitted to the Evanston Hospital at 12 M., April 17, 1944. He had been under care for cardiac disease for some time and on April 15 and 16 had had numerous unexplained episodes of transient circulatory and respiratory arrest, one of which lasted as long as ninety seconds. On the evening of April 16, sometime after 4, a vague sense of distress was present in the left leg. The leg felt cooler to the patient than the opposite leg, but at 8 the pulses in the foot were palpable. By morning only the upper two inches of femoral artery pulsated freely. In view of this femoral embolus developing several hours after the last episode mentioned above, the impression was that the previous episodes had been due to a ball valve thrombus in the left auricle which temporarily occluded the mitral orifice.

On entering the hospital there was a definite arrest of pulsation in the femoral artery at the level of the bifurcation, about 3 cm. below the inguinal ligament. Although the foot was not marble white, there was a definite line of demarcation in the middle of the calf below which the leg was mottled. There were no pulses in the foot, but the foot was pink; the superficial veins were not collapsed totally. The patient was able to move the toes of the foot very slightly. The clinical impression at the time was that an embolic occlusion of the superficial femoral artery had occurred but that in some way partial collateral circulation had been maintained in the rest of the leg. Five cubic centimeters of heparin had been given at 10:30 A.M. In spite of the limited circulatory efficiency, embolectomy was decided upon not only because of the patient's pain, but because of the danger of subsequent thrombosis peripheral and central to the embolus which would result in occlusion of the artery.

Under local anesthesia the femoral artery was exposed. The profunda femoris artery was seen to be almost again as large as the superficial femoral, and it was pulsating at the time. An embolus  $2\frac{1}{2}$  cm. long and about  $\frac{1}{4}$  cm. in diameter was removed from the superficial femoral artery. The embolus had apparently gone well down into the superficial femoral, and the proximal end had only partially occluded the profunda. There was good retrograde bleeding from the superficial femoral before the embolus was removed and very heavy bleeding from above after the embolus had been extracted. The femoral vein was not ligated. After the closure of the arteriotomy there was excellent pulsation in all vessels palpable in the wound.

Pulses in the foot did not return postoperatively but the patient had less pain in the calf.

At the end of the week the patient was able to move the leg with comfort and, although no pulses had returned to the arteries of the foot, it was warm. Heparin and dicumarol had been used in addition to the intermittent venous compression.

Since there was no pallor of the extremity and since at the time of operation the distal superficial femoral seemed totally patent, no antispasmodics aside from papaverine were used.

The patient died suddenly during the night two and one-half weeks after the embolectomy. The preceding day he had had full use of his leg, and all therapy had been discontinued.

*Comment.*—The successful outcome of this patient's limb may be attributed to a combination of factors in addition to the underlying cardiac care. There was a fairly good collateral circulation during the time the embolus was lodged in the femoral artery, heparin was used preoperatively, the embolus was removed easily, and the postoperative care combined anticoagulants, intermittent venous compression, and antispasmodics.

It is of interest to point out that the patient had a temperature of over 102° F. postoperatively which required three days to disappear. This temperature may have represented absorption of toxic material which resulted from the inadequate blood supply to the periphery.

The authors wish to acknowledge the cooperation of the Attending Staff of the Cook County Hospital in allowing them the courtesy of seeing the patients in this series who were in the Cook County Hospital.

The authors wish to take this opportunity of expressing their gratitude to the House Staff at the Cook County Hospital for their help in controlling the heparin therapy.

#### REFERENCES

1. Atlas, Lawrence N.: The Management of Acute Embolic Occlusion of the Arteries of the Extremities, *Surg., Gynec. & Obst.* 74: 236-239, 1942.
2. Crafoord, C.: Heparin as a Prophylactic Against Postoperative Thrombosis. *Acta med. Scandinav.* 107: 116-121, 1941.
3. Danzis, Max: Arterial Embolectomy, *Ann. Surg.* 98: 249-272, 422-437, 1933.
4. Dickinson, Arthur M.: Embolism of the Peripheral Arteries, *Am. J. Surg.* 57: 508-512, 1942.
5. Griffiths, D. Le.: Arterial Embolus, *Lancet* 2: 1339, 1938.
6. Heanley, Lawrence: Arterial Embolectomy, *Lancet* 1: 696, 1939.
7. Herrmann, George R., Willis, J. S., McKinley, W. Frank, and Karotkin, Lester: Embolus and Secondary Thrombosis of the Bifurcation of the Aorta, *Am. Heart J.* 26: 180, 1943.
8. Jorpes, Eric: Pure Heparin for the Prevention and Treatment of Thrombosis, *Acta med. Scandinav.* 107: 107-115, 1941.
9. Key, Einar: Embolectomy on the Vessels of the Extremities, *Brit. J. Surg.* 24: 350-361, 1936.
10. Lewis, Thomas: Pain as an Early Symptom of Arterial Embolism and Its Causation, *Clin. Sc.* 2: 237-251, 1936.
11. Lindgren, Stig, and Wilander, Olof: The Use of Heparin in Vascular Surgery, *Acta med. Scandinav.* 107: 148-160, 1941.
12. Linton, Robert R.: Peripheral Arterial Embolism, *New England J. Med.* 224: 189, 1941.
13. Lund, McKettrick, and Allen: Quoted by Pratt,<sup>22, 23</sup>
14. Lund, Charles C.: Treatment of Embolism of the Greater Arteries, *Ann. Surg.* 100: 880-909, 1937.
15. MacFarlane, J. A.: Multiple Emboli Treated Surgically, *Brit. M. J.* 1: 971, 1940.
16. McClure, Roy D., and Harkins, Henry N.: Recent Advances in the Treatment of Peripheral Arterial Embolism, *SURGERY* 14: 747, 1943.
17. Murray, D. W. Gordon: Embolism of Peripheral Arteries, *Canad. M. A. J.* 35: 61-66, 1936.
18. Murray, D. W. Gordon: Aortic Embolectomy, *Surg., Gynec. & Obst.* 77: 157-162, 1943.
19. Murray, D. W. Gordon, and Best, Charles H.: Use of Heparin in Thrombosis, *Ann. Surg.* 108: 163-177, 1938.
20. Neuhoft, Harold: Embolectomy With Partial Arterial Occlusion for Embolism of the Extremities, *Ann. Surg.* 96: 44, 1932.

prehensive he had no complaints. There was no change in the shrunken abdominal mass. Suddenly, without warning, he vomited copious amounts of blood and died.

*Autopsy.*—The gastrointestinal tract was filled with blood. Careful search showed no lesion in the stomach or first portion of the duodenum. There was a pin-point opening in the third portion of the duodenum which connected directly with the aorta about  $\frac{3}{4}$  inch above the aneurysm. Between this point and the aneurysm was a solid ring of tissue of cartilaginous consistency about  $\frac{1}{4}$  inch in diameter, totally occluding the aorta. On the right side of the vessel just above this constriction was a new small aneurysmal dilatation filled with laminated clot. Two strands of silk were found incorporated in the tissue at the lower end of the constriction. The aneurysm was flat, about one-half its previous size, and on opening it, old organized clot was found. There was no circulation within it.

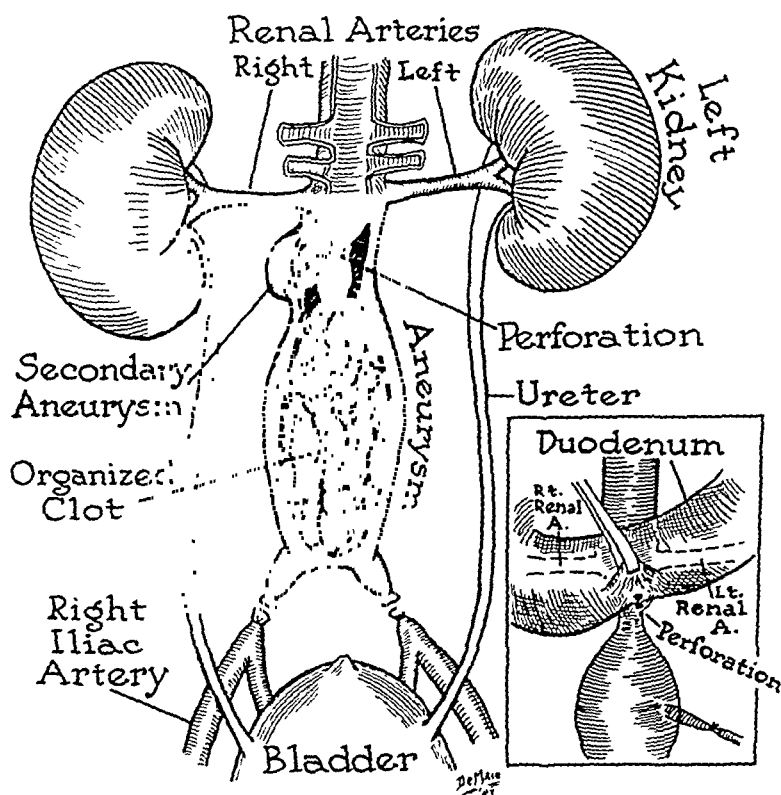


Fig. 4.—Autopsy specimen showing perforation into duodenum just proximal to upper rubber band at edge of small new aneurysm. White area is fibrous tissue of cartilaginous consistency which developed in region in which bands were placed. There is no lumen through this area.

The stumps of the common iliacs attached to the aneurysm were also filled with old clot. The distal common iliacs were both filled with organized clot, as were the external iliacs down to the femorals. The epigastrics were competent but not dilated. There were many small vessels which could be seen coursing over the pelvic peritoneum. There was no evidence of diminished blood supply to the sigmoid colon. Sections of the aorta showed syphilitic aortitis. The heart was not abnormal.

*Comment.*—Grossly, there was no evidence of the rubber bands. Microscopic sections disclosed that they had disintegrated and had become incorporated in the constricting scar tissue. It seems evident that the upper edge of the proximal

band had weakened the aortic wall. This deterioration had resulted in the aneurysmal dilatation on the right side and the eventual perforation on the anterior surface of the vessel. It seemed obvious that the collateral circulation had been maintained by branches from the hypogastric vessels. In spite of the adverse outcome of the case, it seemed remarkable that satisfactory circulation to the limbs could have been maintained after ligation of both common iliac arteries and the aorta above the inferior mesenteric artery. The large bowel undoubtedly obtained its blood supply from anastomoses with the branches of the middle colic artery. It must be concluded that the circulatory system possesses an amazing power of adaptability, at least in the lower part of the body, if partial interruption of the blood flow is accomplished as a preliminary measure. To my knowledge this is the first time that the aorta and both common iliacs have been ligated in the human being, with success as regards adequacy of the circulation.

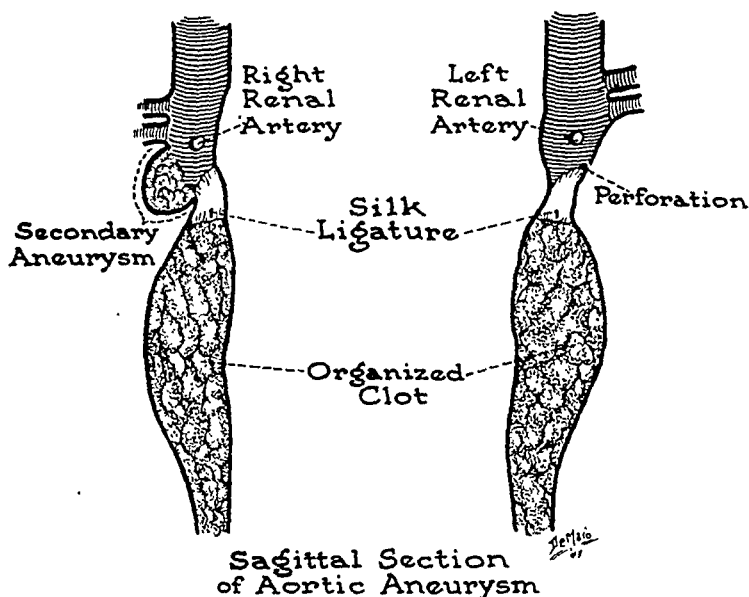


Fig. 5.—This is a sagittal section through the aorta and aneurysm showing the organized clot in the shrunken aneurysm, constricting fibrous tissue, silk ligatures, new aneurysm, and point of perforation. Also note relation to renal arteries.

#### ANALYSIS OF PREVIOUS CASES

Vaughan,<sup>4</sup> in 1921, reported partially occluding the aorta below the origin of the inferior mesenteric artery for an aneurysm lying above the origin of the superior mesenteric artery in a 39-year-old man. At Halstead's suggestion he used cotton tape and the patient survived for two years and one month. It is difficult to see how this procedure would have a beneficial effect on an aneurysm proximal to the ligation. Rather one would expect a deleterious effect.

In April, 1923, Matas<sup>5</sup> completely occluded the aorta below the inferior mesenteric artery in a woman, aged 28 years, for a leaking aneurysm of the terminal aorta. This was the first reported clinical cure of an aortic aneurysm by proximal ligation. The aorta was occluded by two cotton tapes. For the first week the patient was in a precarious condition, which was relieved, in the opinion of Matas, by the relaxation of the tapes and return of partial circulation through



the aneurysm. She died of progressive pulmonary tuberculosis one year, five months, and nine days after ligation, and at autopsy there was complete consolidation of the clot and shrinkage of the aneurysm. It is probable that a preliminary partial ligation would have avoided the stormy postoperative course of this patient. This, of course, would not have been feasible because the aneurysm had already begun to give way.

Watts,<sup>6</sup> in September, 1923, described a woman 60 years of age with a lower abdominal aneurysm treated by partial occlusion with cotton tape below the superior mesenteric artery. The patient lived three and one-half years. In 1926, Brooks<sup>7</sup> ligated the aorta distal to the inferior mesenteric artery in a man aged 59 years. The artery was completely occluded with fascia lata and heavy silk distal to the fascia. Brooks was convinced that considerable collateral circulation had been built up before operation, accounting for the absence of symptoms in the extremities following operation. Death from intestinal obstruction resulted after three months. Autopsy showed the aneurysmal sac completely obliterated by clot, and the aorta completely obstructed at the site of ligation by a well-organized thrombus.

LaRoque,<sup>8</sup> in 1930, reported partially occluding the distal abdominal aorta with tape and heavy silk in treating an aneurysm of the right common iliac artery in a patient 30 years of age. She was alive and greatly improved at the end of fourteen months.

The case described by Bigger,<sup>2</sup> in 1940, is unique because of the rarity of the lesion and the truly remarkable skill which effected a cure. He treated a ruptured aneurysm of the lower aorta, resulting from a gunshot wound in a youth 25 years of age, by complete proximal ligation with fascia lata and subsequent endoaneurysmorrhaphy. The feature of interest is that there was complete paralysis of both lower extremities of about two weeks' duration following complete occlusion, this gradually clearing over a two-week period. Obviously, it was necessary to occlude the aorta completely above the fistula because of the acute hemorrhage. However, the case demonstrated that complete occlusion, even in a healthy young adult, should be avoided if possible.

In 1940, Elkin<sup>3</sup> described partial occlusion of the aorta distal to the inferior mesenteric with cotton tape in a male, aged 50 years, with relief in symptoms and decrease in size of the aneurysm.

#### DISCUSSION

Thus we see that of these seven patients only three had total occlusions done in one stage. In the other four operative survivals partial occlusion had been done. In two of the cases of total occlusion in one stage, those of Matas and Brooks, collateral circulation existed at the time of operation. Matas states that collateral had been well established, and Brooks felt that a similar situation—both common iliacs

had been partially obliterated—was responsible for the benign course and cure of his patient. Whether or not collateral was present in Bigger's case is questionable. At any rate, the early postoperative reaction of his patient, paralysis of both extremities, suggested that only his youth and vascular adaptability allowed him to survive. In the early cases from the time of Cooper to 1920, patients who did not die of hemorrhage died of shock. This was no doubt due to the fact that total occlusion in one stage is not well tolerated by man.

The comparatively benign course of the patient I have described after a two-stage complete occlusion of the aorta, would seem to establish the fact that in the region of the lower abdominal aorta, at least, an occlusion in stages is distinctly feasible. It would seem likely also that many older patients could withstand total occlusion in stages from the standpoint of circulatory efficiency.

Gage<sup>9</sup> has stated that "all cases that have survived ligation with tape have demonstrated both clinically and at autopsy that the lumen has been partially restored." Brooks stated in 1926, "ligature of the artery proximal to the aneurysm as everyone knows, is usually not a satisfactory cure of aneurysm." If cure resulted in the cases of Matas and Brooks because both common iliacs were at least partially obliterated, I have shown that these conditions can be produced by deliberately dividing and ligating these vessels. It is difficult to conceive of circulation being re-established in my patient through the cartilaginous ring found proximal to the aneurysm, and of course, circulation from below could not be re-established with the iliacs divided. It would seem that proximal obliteration could very well cure aneurysms if material or a method could be obtained whereby healing of the vessel by fibrosis would occur without weakening of the vessel by the pressure of an occlusive band.

The pressure of the proximal rubber band in the case I have reported undoubtedly caused the small aneurysm just above the band on the right side of the aorta. Likewise pressure of the band caused the eventual perforation. Furthermore, in 28 of 75 dogs operated upon by Owings, the rubber bands cut through the vessel. It would seem fair to conclude that rubber is not a safe material with which to occlude the aorta. Owings states that it does not seem likely that aneurysms in man can be successfully treated by proximal ligation, because of the likelihood that the vessel walls are diseased and unable to tolerate ligation. It is worthy of note, however, that in the cases of Vaughan, Matas, Watts, LaRoque, and Elkin, cotton tape was used, and in none of these did the tape cut through the vessel wall. Matas demonstrated histologically that cotton tape is well tolerated by the tissues of the aortic wall. In his case no ulcerative, thrombotic, or necrotic changes were observed beneath the tape. Three of these cases were due to syphilis of the aorta and presumably the vessel was not entirely healthy. These patients were not all young—one was

39 years of age, one 59, and one 60. The patient I have reported was 49 years old. These facts suggest that cotton tape is the best material for proximal ligation at the present time. Tape could certainly be used in the preliminary partial ligation, and it is likely that cure would result with a second occluding ligation with tape and division and ligation of the iliaes. It seems clear, however, that a more physiologic technique should be developed for permanently occluding the vessel than the use of strangulating ligatures. When we consider the aorta as a living structure it is immediately realized that the blood supply on which we are dependent for repair and permanent healing has been compromised by this procedure. Possibly a preliminary partial ligation with cotton tape, then division of the vessel at the second stage, traumatizing of the intima and suturing its surfaces together with parallel rows of fine sutures, or some similar procedure, would be the answer. J. S. Horsley, Jr.,<sup>10</sup> has shown that vessels heal with greater degree of fibrosis when they are divided, receiving additional nutrition from the surrounding tissues. This problem still awaits solution.

#### SUMMARY AND CONCLUSIONS

A case is reported in which the aorta was occluded in stages by rubber bands proximal to an aneurysm with division of both common iliac arteries. The patient lived approximately five months from the time of the first ligation. Seven cases of aortic ligation are reviewed. Of these, there were four partial and three total occlusions. Of the three total occlusions, three patients had collateral established at the time of operation and the third had alarming paralysis of the extremities following ligation, and survived probably because of his youth.

Occlusion of the lower abdominal aorta is feasible. Furthermore, man will tolerate division of both common iliaes after ligation of the aorta. Cotton tape has been demonstrated as the least noxious material for ligation. It seems reasonable that ligation in stages with cotton tape, plus ligation of both iliaes, should cure aneurysms of the lower abdominal aorta.

#### REFERENCES

1. Owings, James C., and Hewitt, John F.: Successful Experimental Ligation and Division of the Thoracic Aorta, *Ann. Surg.* 115: 596, 1942.
2. Bigger, L. A.: Surgical Treatment of Aneurysm of the Abdominal Aorta, *Ann. Surg.* 112: 879, 1940.
3. Elkin, D. C.: Aneurysm of the Abdominal Aorta, *Ann. Surg.* 112: 895, 1940.
4. Vaughan, George T.: Ligation of the Abdominal Aorta for Aneurysm, *Ann. Surg.* 74: 308, 1921.
5. Matas, Rudolph: Aneurysm of the Abdominal Aorta at Its Bifurcation, *Ann. Surg.* 112: 909, 1940.
6. Watts: Reported by Bigger.<sup>2</sup>
7. Brooks, Barney: Ligation of the Aorta; A Clinical and Experimental Study, *J. A. M. A.* 87: 722, 1926.
8. LaRoque, G. Paul: Ligation of Abdominal Aorta for Aneurysm of Common Iliac Artery, *Tr. South. S. A.* 43: 245, 1930.
9. Gage, Mims: Mycotic Aneurysm of the Common Iliac Artery, *Am. J. Surg.* 24: 667, 1934.
10. Horsley, J. S., Jr.: Healing of Arteries After Different Methods of Ligation, *J. A. M. A.* 85: 1208, 1925.

# THE PHYSIOCHEMICAL DISTURBANCE IN A SEVERE BURN\*

BERNARD J. FIGARRA, M.D.,† AND EMIL A. NACLERIO, M.D.‡  
BROOKLYN, N. Y.

(From the Department of Surgery, Kings County Hospital)

## INTRODUCTION

UNIVERSAL interest in the subject of burns has always captivated the attention of surgeons. The voluminous literature on this subject clearly indicates that interest is never waning. The majority of authors writing on this subject concern themselves with definitive treatment, the associated shock, fluid balance, and similar topics. The most neglected phase of the burn problem has been the physiochemical disturbance produced by tissue destruction. The changes reflected in the circulating blood due to severe burns in a human being have been studied rarely. Most of the data known to us have been gathered from animal experimentation. In the treatment of burns the opportunity and facilities were available to us on one occasion for a detailed and continual physiochemical observation of a severely burned patient. In view of the fact that few complete chemical analyses have been made in clinical burns, the following case report was considered significantly valuable.

## CASE REPORT

The patient was a 43-year-old white male employee of a public utility company. While working at the top of a forty-foot pole, his clothing became inflamed from sparks which arose from the wire he was repairing. By the time he reached the ground his clothes were a mass of flames. His clothing was removed and tannic acid applied to the body surface by members of the fire department. He was then taken to the hospital.

On admission the patient was in clinical shock from diffuse burns involving 60 per cent of his body surface. There were third degree burns of both thighs, second and third degree of right arm and forearm, and first and second degree about both ankles. In addition he had a fracture of the left ankle. At this time his temperature was 99.6° F.; pulse, 120; respirations, 26; blood pressure, 90/50.

Nine hours after admission the patient had responded sufficiently from shock to permit treatment of the burn. One hundred cubic centimeters of whole blood were taken for study immediately after entrance. For the first sixteen hours blood chemistry studies were done every four hours. Thereafter complete studies were made every day. On the seventh postburn day the only available vessel for obtaining a blood sample was the internal jugular vein. This was due to the fact that the burn areas prevented the use of many vessels, others became thrombosed, and on that day the patient became edematous.

On the ninth postentrance day the patient's temperature rose to 102° F., and he became delirious. Two days prior to this a toxic erythematous rash became

\*Presentation of this case is made possible through the kindness and cooperation of Ralph F. Harloe, M.D., F.A.C.S., Assistant Clinical Professor of Surgery, Long Island College of Medicine, Brooklyn, N. Y.

†Fellow in Surgery, Lahey Clinic, Boston, Mass.

‡Fellow in Thoracic Surgery, under Dr. R. H. Overholt, Brookline, Mass.

Received for publication, May 12, 1944.

visible on the nonburned skin surfaces. The patient expired on the tenth hospital day in spite of the general therapy of whole blood, plasma, fluids, adrenal cortical extract, vitamins, chemotherapy, proteins, and local treatment of the burn areas.

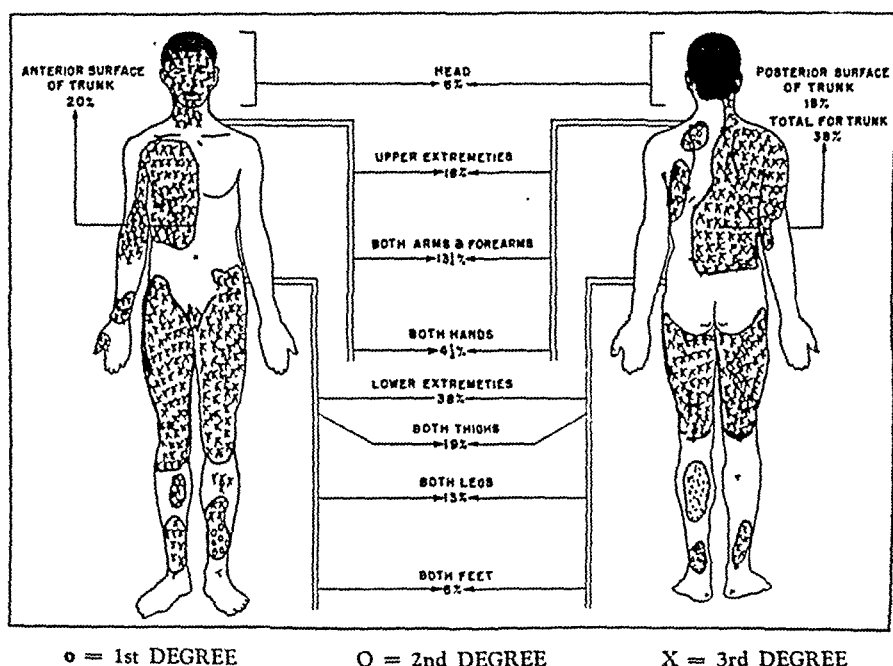


Fig. 1.—Chart illustrating percentage of body surface burned according to degree of the burn.

*Autopsy Findings.*—We were fortunate in this instance to secure an autopsy.\* The anatomic findings were as follows:

1. Primary diffuse third degree burns of the head, chest, back and upper and lower extremities
2. Pyoderma with ulceration
3. Bilateral acute and chronic interstitial pyelonephritis and nephrosis
4. Bilateral adrenal hemorrhage
5. Passive congestion of the liver
6. Hemorrhagic cystitis
7. Acute tracheitis
8. Ulcerative esophagitis
9. Mucosal hemorrhage throughout the gastrointestinal tract
10. Cardiac hypertrophy with right ventricular dilatation
11. Pulmonary edema
12. Chronic cholecystitis with calculi

The significant pathologic findings were revealed in the study of the skin, kidneys, liver, and adrenal glands. Of these four organs the most interesting findings were noted in the kidneys.

Grossly the kidneys were extremely large. The right one weighed 470 Gm.; the left, 380 Gm. The capsule was thin and stripped easily. The underlying cortical surface was reddish brown in color with readily demarcated cortex and medulla. The glomeruli were grossly prominent.

\*Permission for necropsy study was obtained through the efforts of Dr. Robert F. Barber, Professor of Clinical Surgery, Long Island College of Medicine.

Microscopic examination of the kidneys demonstrated the glomerular spaces to be distended with albuminous deposits. The cytoplasm of the tubular epithelium had a ground-glass appearance, especially in the proximal convoluted tubules. Many tubules contained albuminous material. A marked interstitial edema with scattered localized areas of hemorrhage was present. The renal pelvis, medulla, and isolated cortical regions showed dense collections of lymphocytes, plasma cells, and fibrin. The capillaries showed a pronounced dilatation and engorgement.

Pathologic histology of the liver showed a generalized dilatation and engorgement of the sinusoids. The liver cells indicated passive congestion. Lymphocytic nests with occasional polymorphonuclears were seen about the portal region.

The adrenal glands retained their normal histology. However, the zona reticularis of the medulla contained hemorrhagic areas. The cells had a coarse ground-glass appearance. Marked interstitial edema was seen in all the zones of the medulla.



Fig. 2.—Photomicrograph of kidney showing albuminous material in tubules and interstitial hemorrhage. Some tubules contain red blood cells. ( $\times 100$ .)

#### GENERAL DISCUSSION ON CHEMICAL CHANGES

It has been generally accepted in the past that in extensive burns a toxic state results due to injurious elements produced by burned tissues. The quantity of liberated toxic substances which passed into the circulation was believed to be proportional to the extent of the burn. The exact nature of this toxic substance has never been determined. Formerly it was thought to be derived from the albumin of the cell and was suspected to be a polypeptide. Death was attributed to toxic physiopathologic alterations in the internal organs due to this proteid substance.

Our experience with burns has led us to believe that the question cannot be answered simply by stating that toxicity is the cause of

physiologic dysfunction. Heretofore minimal consideration has been given to the physiochemical changes in burns. In 1924 Davidson studied intensively the sodium chloride metabolism in burns.<sup>1</sup> This was the first time that an evaluation of the blood chemistry found a



Fig. 3.—Section of liver demonstrating central veins congested with red blood cells. Collections of lymphocytes are seen about portal areas. Evidence of passive congestion is present. (X100.)

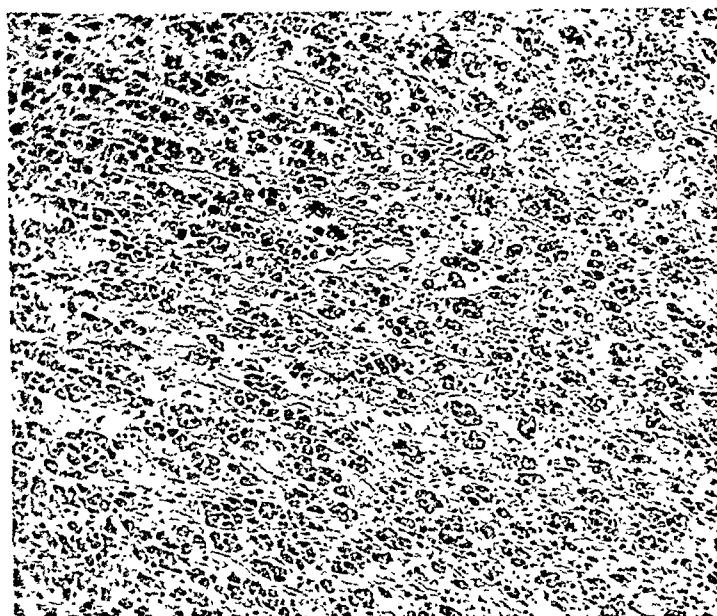


Fig. 4.—Adrenal gland showing marked hemorrhage in the zona reticularis. (X100.)

prominent place in the discussion of burns. He found a significant lowering of the chlorides which was believed to be due to a lowering of plasma chlorides below the renal threshold rather than to a primary kidney change. It was further observed by him that the chlorides did not fall immediately after the burn but diminished progressively during the first few days.

Harkins believes that fluctuation in the blood chloride values is more pronounced than blood sugar changes.<sup>2</sup> Chloride changes are attributed to a selective permeability of the burned capillaries for smaller molecules. Scudder studied a severe burn case as to chlorides.<sup>3</sup> These values were slightly above normal on admission of the patient and were so maintained. On the fourth day a decrease below normal occurred. By the eighth day, the chloride values reached a small peak. Roughly, the changes in chloride concentration paralleled the fluctuations in sodium.<sup>3</sup> Accentuated interest has been given to sodium in cases of severe burns. Fox, in a recent publication, has stressed the importance of sodium in the rational treatment of the burned patient.<sup>4</sup>

The alterations in plasma protein values with a shift in the albumin-globulin ratio and its association with the production of edema have been emphasized recently. This has been attributed to the loss of blood fluids through the burn areas. It is believed that in such cases albumin may be lost in slightly greater quantities than globulin.<sup>2</sup>

Observation of the blood chemistry during burns by Beck and Powers was the first evaluation of the nonprotein nitrogen.<sup>5</sup> These observers noted an increase in nonprotein nitrogen. In later postburn studies a rise in creatinin and uric acid was recorded. The increase in these products was attributed to renal tubular damage.<sup>6</sup>

All writers experienced in the management of burns recognize the initial hyperglycemia. This elevation of blood sugar has been attributed to adrenal stimulation. The rise and fall of the blood sugar level parallels the degree of hyperadrenalism. Fatigue of the adrenal glands and the exhaustion of adrenalin secretion are reflected in the diminution and rapid fall into a lethal hypoglycemic state.

Evaluation of blood concentration and acidosis have been stressed in burns. Hemoconcentration almost always follows a burn. This state results from fluid loss from the burn surfaces and the retention of fluids plus crystalloids within the body tissues. Such hemoconcentration is either a cause or a result of some serious disturbance in the physiologic regulation of the human body.<sup>2</sup> Since 1903, when Stockis called attention to a decrease in the carbon dioxide content of the blood following experimental burns, the tendency toward acidosis in these patients with burns has been recognized.<sup>7</sup> This finding has been corroborated by many subsequent investigators. Lam (1941) observed a decreased carbon dioxide combining power as low as 20 to 25 volumes per cent in patients who died.<sup>8</sup> These are among the lowest values recorded in the literature. He further observed no beneficial effect from the administration of sodium bicarbonate to such patients.



Thus in brief is the present concept of the physiochemical background in diffusely burned patients. The elucidation of this problem has been accelerated in recent decades, although the answer has not been reached as yet. Many burn researchists have given minimal consideration to this problem in spite of the fact that interest in blood chemistry alterations in burns was recorded as early as 1863.<sup>5</sup>

#### PROBLEM OF FLUID BALANCE

The major concern in the treatment of burn shock is the administration of intravenous fluids that will restore the blood volume and its physiologic components to near normal level. The preference for plasma is based upon the fact that extensive burns are followed by exemia and cellular concentration of the blood. Harkins devised a simple method of calculating plasma dosage. His formula is to give 100 c.c. of plasma for every point the hematocrit is above the normal of 45.<sup>2</sup>

English authors have employed sodium bicarbonate infusions with the objective of combating acidosis. When this solution is employed, the danger of azotemia from alkalosis is to be remembered. It has been stated that "Intravenous injection of crystalloids such as sodium chloride should be avoided for they are quickly lost from the circulation, carrying with them a part of the plasma."<sup>15</sup> A statement such as this is worthy of notation even if it is open to debate.

As a result of hemoconcentration, acidosis, and sluggish pulmonary circulation, oxygenation of arterial blood becomes increasingly inefficient. "Tissue anoxia with a compensatory hyperventilation occurs which increases the rate of fluid loss. This in turn produces a reduction in plasma volume and the hemoconcentration increases."<sup>16</sup> With this thought in mind, "the beneficial effect of transfusions in burned patients in all probability is due as much to the additional oxygen-carrying material thus supplied as to the replacement of lost serum protein and blood electrolytes."<sup>16</sup>

The use of whole blood has added value in the treatment of the anemia associated with burns. The development of secondary anemia occurs after the first or second week, especially in third degree burns. These burns with raw granulating surfaces are associated with blood loss due to infection and small local hemorrhages. Another etiological factor in the production of the anemia may be a toxic depression of the bone marrow. As a result of the disturbance in capillary permeability in these traumatized tissues and in the gastrointestinal tract, an extravasation of blood serum with many red cells occurs. Where diffuse gastrointestinal hemorrhage occurs, an additional loss of blood results.

The work of Schievers indicates that due to red cell destruction or other factors, a decrease in red blood cells occurs soon after a burn.<sup>17</sup>

"The important fact about Schievers' data is that the decrease in blood volume was greater than the plasma loss would account for and must be accompanied by a decrease in red cells as well. It has been said that transfusion is not indicated in burn shock since the blood is already concentrated. It is to be pointed out that the presence of a high blood concentration would not be a valid argument against transfusion. This is true because the donor blood is dilute in comparison to the patient's blood."<sup>2</sup>

#### CASE DISCUSSION

With the aforewritten background we are prepared to discuss the information revealed in the data acquired from the case presented.

Our observations have led us to believe that an evaluation of the blood chlorides is extremely important. It cannot be definitely stated that the most important ion is the chloride ion or whether the sodium ion is the one to be stressed. Scudder emphasizes the fact that a rise and fall in chloride values parallels the alterations in sodium values.<sup>5</sup> Fox has stressed most emphatically that the sodium ion plays the master role in the electrolyte balance.<sup>4</sup> Which ion has the major role cannot be stated at present. Immediate treatment of incipient burn shock with chlorides and sodium may be changed according to the work of the authors just mentioned.

In the case presented changes in the blood chlorides were not very remarkable. However a significant fall in value occurred on the fifth postburn day (from 600 to 480 mg. per cent). This fall on or about the fifth day has been noted by other observers.<sup>3, 4, 18</sup> This suggests that the critical period in ionic disturbance may occur on or about that day. Such profound alterations may indicate a "break" in the biochemical compensation on the part of the human body. On this day especially an evaluation of the blood chlorides and sodium seems to be of paramount importance. The administration of large volumes of sodium on this day may be the necessary factor in the prevention of biochemical decompensation.

As a generality the value of sodium paralleled the chloride determination. All the sodium values on all occasions were below the normal of 142. On the fifth postburn day a decided fall in the plasma sodium was noted for the first time: The value was 129.2. On the eighth and ninth days the values were lower: 122.4 and 123.7, respectively. The fifth day corresponds to the period when the biochemical decompensation occurred. On the eighth day clinical evidence of the patient's inability to maintain an adequate water balance was visible.

On the eighth postentrance day the patient developed marked anasarca. This production of edema again reveals the importance of sodium and blood protein. No significant early alteration occurred in the total protein value, although a slight fall was recorded. Three

days before the onset of clinical edema a fall in total protein to 3.5 Gm. was found. A low value persisted to the eighth hospital day. In this instance a fall in blood protein occurred several days before the onset of visible edema. A daily evaluation of the albumin-globulin ratio may warn against incipient edema. With this knowledge available, edema may be avoided by means of protein replacement therapy.

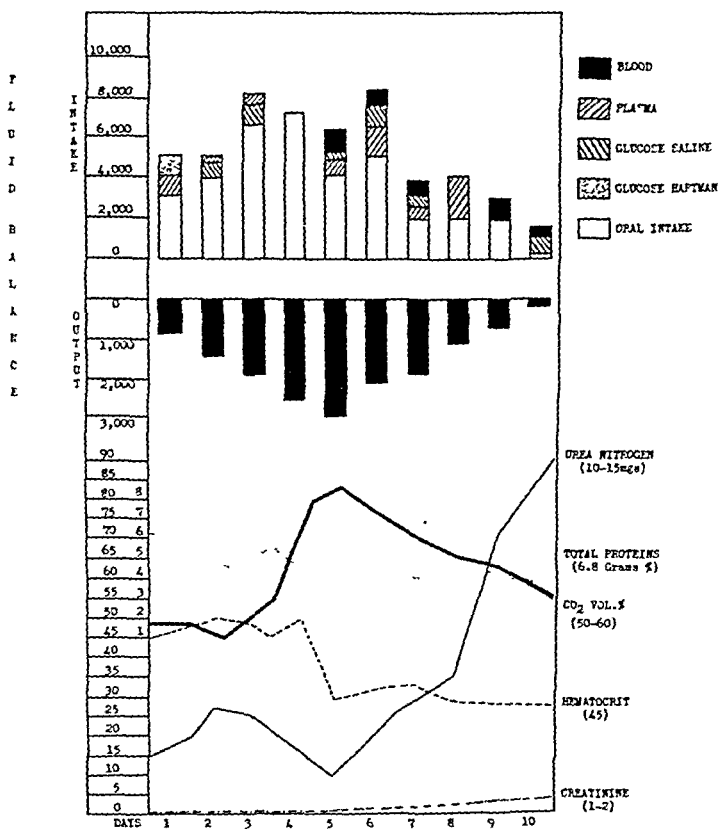


Fig. 5—Composite chart illustrating fluid balance in association with blood chemistry values and hematocrit studies

Another index of protein loss is estimated by the nitrogen excreted. Estimation of the blood urea nitrogen demonstrated a gradual, then a rapid, daily rise, finally reaching 90 mg. per cent on the tenth post-burn day. The nitrogen excretion was very high so that the patient's nitrogen balance could not be restored even though large volumes of proteins were administered. In this patient the total nitrogen loss could not be calculated exactly. This was due to the fact that much nitrogen was lost through the feces and through the burned skin areas. Toxic destruction of protein is usually attributed to fever in the burned patient. In addition to fever, other factors associated with nitrogen metabolism must be sought for protein destruction in diffuse burns.

TABLE I  
RESULTS OF DAILY BLOOD STUDIES AND SPECIAL TESTS PERFORMED IN CASE PRESENTED

DAYS	TIME	CHLORIDE	PLASMA SODIUM	SUGAR	TOTAL PROTEIN	ALBUMIN	GLOBULIN	CREATININE	UREA N	UREA	CO <sub>2</sub>	Hb. (gm.)	R.B.C.	W.B.C.	HEMATOCRIT	CEPHALIN FLOCCULATION	CHOLESTEROL	CHOLESTEROL ESTERS	ICTERUS INDEX	P.S.P. TEST
1	4:00 P.M.	608	140.8	561	6.3	4.4	1.9	1.50	18.1	38.7	48.5	13.5	4.6	22,000	45		180	110		
	7:00 P.M.	615	135.4	336					18.8	40.2		15.0	4.6	23,000	52					
	12:00 P.M.	605	133.8	298					18.6	39.6			4.8				184	102		
2	2:00 A.M.	602	135.4	223	5.8	3.7	2.1	1.90	28.2		41.9	15.5	3.8	25,000	48		172	98		
	10:00 A.M.	600		151	4.7	3.1	1.6		27.2		48.5	10.5	3.8		50					
3	8:00 A.M.	600	133.8		5.7	3.8	1.4		27.8			11.0	3.6		45					
	3:00 P.M.											10.0	3.2	8,400	48		163	98	3.5	
4	10:00 A.M.	480	129.2	102	3.5	2.4	1.1	1.35	11.3		84.3	10.5	3.4		30	Neg.			3.5	
5	7:30 A.M.	565		132				1.35	15.0				2.9							
	4:00 P.M.	511	134.2	176	4.4	2.6	1.8	1.50	15.9		78.7	10.0	2.2		32	Neg.				
6	7:30 P.M.	507	131.2	116	4.0	2.7	1.3	1.75	30.6		76.8	11.0	2.5	10,100	33	Neg.				
7	7:45 A.M.																			
8	7:30 A.M.	480	122.4	83	4.3	3.0	1.3	2.30	38.2		67.3	10.0	2.480	12,000	29	Neg.	160	57		No dye
9	7:45 A.M.	494	123.7	123	4.5	2.9	1.6	3.60	69.0		61.7	10.0	2.5			Neg.	132	57		No dye
10	7:45 A.M.			211				4.00	90.0		54.1	10.0	3.100	12,600	28	Neg.				No dye

A second observation in reference to the blood nitrogen status in this patient was that it pointed to a renal derangement. A preuremic state may have existed in spite of the adequate output of urine. Urinalyses failed to reveal any unusual findings.

The disturbed carbohydrate metabolism in this patient was reflected in the study of the blood sugar. A review of the blood studies demonstrates an immediate hyperglycemia of 561 mg. per cent. The hyperglycemia gradually diminished, returning to normal eighteen hours after admission. The immediate hyperglycemia following this severe burn suggests that glycogenolysis can occur which may deplete the liver of its glycogen reserve. It is logical, therefore, to administer glucose in order to replenish the liver glycogen, in spite of the existing hyperglycemia.

Associated with the blood sugar determinations are the adrenal relationship and the problem of acidosis. The parallelism between the fluctuating blood sugar and the pathologic changes in the adrenal glands has been studied intensively by others.<sup>13</sup> The gradual-developing adrenal insufficiency leads to blood pressure alterations in addition to disturbed carbohydrate metabolism. Often this irreparable fall in blood pressure occurs on or about the fourteenth day and is a contributing death-producing factor due to adrenal exhaustion.

The problem of acidosis in burns gives rise to the assumption that the disturbed carbohydrate metabolism may be interpreted as the underlying cause. The possibility presents itself that the so-called burn "toxicity" may be an expression of some intermediary metabolism leading to acidosis.

In our patient the carbon dioxide combining power eight hours after admission was 48.5 per cent. Eight hours later the value was 41.9 per cent, showing a tendency toward acidosis. This tendency continued. For the third and fourth postburn days (a week end) no facilities were available for carbon dioxide determinations. At this time the patient was given citrocarbonate, 1 dram every four hours for twenty-four hours, plus 100 c.c. of lactated Ringer's solution. On the fifth postburn day (a Monday) the carbon dioxide combining power rose to 84.3 per cent. This demonstrated that our patient had alkalosis. With the knowledge of Lam's work at our disposition, we were at a loss to explain this phenomenon,<sup>8</sup> for it will be recalled he wrote that no beneficial effects could be found by administering carbonates in burn acidosis. It was then thought that the fifth day may again be incriminated as the critical period in the ability of the body to combat a physiochemical decompensation.

As a general statement it may be said that hemoconcentration develops soon after an extensive burn. The alteration in the blood concentration and dilution was often considered as a prognostic sign. These changes in concentration and dilution have formed a basis for the administration of plasma. In the management of this patient we

followed as far as possible the method of Harkins.<sup>2</sup> The hematocrit demonstrated hemoconcentration for the first five days. Thereafter hemodilution was present until death. Hematocrit evaluations alone are not accurate indices. Such evaluations are more useful when employed in association with a red cell count, hemoglobin determination, and a knowledge of the urinary output.

Blood picture studies revealed the onset of anemia within eighteen hours after injury. Hemoglobin values fell from 15.5 Gm. to 15 Gm. to 10.5 Gm. within these hours. During this time the hematocrit failed to demonstrate any deviation from the normal ratio.

On the sixth postburn day melena was noted for the first time. In view of the autopsy findings this can be attributed to gastrointestinal hemorrhage. On the seventh postburn day the patient's bowel movements were very bloody and continued to be so until death. On the seventh day a rash developed over the normal skin surfaces. Dermatologic consultation labeled the rash as a toxic erythema. The question is brought forward as to whether or not this toxic erythema was not subcutaneous hemorrhage corresponding to gastrointestinal hemorrhage. When the initial rectal bleeding was observed, a marked anemia was present. The red count was 2,200,000; the hemoglobin, 10 Gm. Both values were persistently low until death.

The low blood count and hemoglobin indicated that the oxygen-carrying capacity of the blood was one-half its normal potentiality. On the sixth day the patient had respiratory distress which demanded oxygen therapy. This distress was attributed to ischemic anoxia resulting from the lowered red cell volume.

Observation of this patient has shown that a sharp and sudden rise or fall in the red cell count and hemoglobin should suggest the necessity for additional fluids, plasma, or whole blood as indicated. Over a ten-day period this patient received a total fluid intake amounting to 41,920 c.c. Of this total, 16,200 c.c. were given parenterally. The solutions used were as follows:

Glucose in saline	5,000 c.c.
Glucose in Hartmann's	1,200 c.c.
Plasma	6,900 c.c.
Whole blood	3,100 c.c.
	<hr/>
	16,200 c.c.

Notwithstanding the continual observation and treatment of this patient, he succumbed to the injury ten days after the accident. In a search for the cause of the patient's death the five major causes of death in severe burns were considered. These are shock, infection, hepatic insufficiency, adrenal exhaustion, and renal failure. Death in this instance could not be assigned to shock or infection. The cephalin flocculation test on seven occasions was negative. The icterus index was 3.5 on three successive days; a slight fall in cholesterol esters was

noted. These affirm that the liver function was apparently satisfactory. Autopsy studies substantiated the fact that the liver was not the cause of death.

Death may be attributed to adrenal exhaustion and renal failure. These organs are indicted in view of the blood chemistry studies, the phenosulfonphthalein test on the last four days of life, and the pathologic changes found in these organs at necropsy.

This case has emphasized that the intelligent management of the severely burned patient demands daily biochemical diagnostic studies. The facility with which an altered physiochemical state occurs merits constant checking of the blood chemistry. Therefore it can be stated that biochemical determinations are equally as important as therapy and the definitive treatment of the severely burned.

#### SUMMARY AND CONCLUSIONS

1. Metabolic and chemical data are presented in a case involving fatal burns.

2. This case illustrates sodium chloride changes, hypoproteinemia, destruction of body protein, alterations in carbohydrate metabolism, and hemoconcentration.

3. The acidosis which usually accompanies the burn syndrome was absent. An unexpected alkalosis occurred following the administration of citrocarbonate on the fifth postburn day.

4. Emphasis is placed upon a study of the blood chemistry on or about the fifth day. At this time a break in the biochemical harmony occurs. This discord is manifested in an elevation of the end products of nitrogen metabolism associated with a fall in serum proteins, plasma sodium, and blood chlorides.

5. In the treatment of this patient, 16,200 c.c. of fluids were administered parenterally. Of this amount, 6,900 c.c. were plasma and 3,100 c.c. were whole blood.

6. Death on the tenth day was attributed to adrenal exhaustion and renal failure.

7. The major factor leading to the cause of death in burns has not been established satisfactorily. It is believed that a severely burned patient dies of physiologic exhaustion. Therefore a study of the organs involved in this disturbed physiology (liver, kidneys and adrenals) will assist in the elucidation of the problem of the unknown lethal factor.

8. Herein lies the intrinsic value of serial studies of the physiochemical changes in the burned body as reflected in altered blood chemistry.

9. The exhaustion of the aforementioned basic physiologic organs may be the cause of death when, after the second week, the patient seems to be improving.

10. This somatic distress is emphasized because during the third week the initial danger apparently has been overcome. The anxious

surgeon considers the patient sufficiently improved for a skin graft. However, the disturbed chemistry has not been restored. In the presence of this metabolic discord, the administration of an anesthetic plus the surgical procedure may be sufficient to cause death.

11. In view of the presented facts, the thought is advanced that repeated examinations of the blood are necessary guides to the intelligent management and treatment of the severely burned patient. Without these studies one cannot know whether or not the desired results are being achieved.

12. Whenever possible the laboratory studies should include a daily red blood count, hemoglobin, urinalysis, and blood chemistry determinations (proteins, sodium, chlorides, nonprotein nitrogen, icterus index, and carbon dioxide combining power).

We wish to express our gratitude to Dr. S. Potter Bartley, Assistant Clinical Professor of Surgery, Long Island College of Medicine, for his guidance in the clinical management of the patient described in this report. Additional indebtedness is acknowledged to Mr. John C. Knight for his cooperation in the production of the charts and photomicrographs.

#### REFERENCES

1. Davidson, E. C.: Sodium Chloride Metabolism in Cutaneous Burns and Its Possible Significance for a Rational Therapy, *Arch. Surg.* 13: 262-277, 1926.
2. Harkins, Henry N.: The Treatment of Burns, Springfield, Ill., 1942, Charles C Thomas.
3. Scudder, J., and Elliott, R.: Controlled Fluid Therapy in Burns, *South. Med. & Surg.* 104: 651-658, 1942.
4. Fox, C. L.: Oral Sodium Lactate in the Treatment of Burn Shock, *J. A. M. A.* 124: 207-212, 1944.
5. Beck, C. S., and Powels, J. H.: Burns Treated by Tannic Acid, *Ann. Surg.* 84: 19-36, 1926.
6. McIver, M. A.: A Study in Extensive Cutaneous Burns, *Ann. Surg.* 97: 670-682, 1933.
7. Stockis, E.: Recherches expérimentales sur la pathogenie de la mort par brûlure, *Arch. internat. de pharmacodyn. et de therap.* 11: 201-299, 1903.
8. Lam, C. R.: The Chemical Pathology of Burns, *Surg., Gynec. & Obst.* 72: 390-400, 1941.
9. Rudler, J. C.: Les accidents précoces consécutifs aux brûlures superficielles étendues: Pathogénie et traitement. Paris, 1935, Librairie Luis Arnette.
10. Rabboni, F., and Cacioppo: Recherches sur la glycémie, *Cultura Medica Moderna*, 1934. Quoted by Rudler.
11. Zinek, K. H.: Morphological Lesions of the Liver and Kidneys and Hepato-Renal Insufficiency After Burns, *Klin. Wchnschr.* 19: 78, 1940.
12. Martin, J. D., Jr.: Clinical and Experimental Studies of Burns, *J. M. A. Georgia* 27: 39-46, 1938.
13. Kogan-Yasniy, V. M., and Altgauzen, A. Y.: An Injury to the Suprarenals and Disturbances of the Carbohydrate Metabolism in Burns, *Vrach. delo.* 20: 88, 1938.
14. Cope, O., and Rhinelander, F.: The Problem of Burn Shock Completed by Pulmonary Damage, *Ann. Surg.* 117: 915, 1943.
15. Johnson, L. W.: Medical and Sanitary Care of the Civilian Population Necessitated by Attacks From Hostile Aircraft, *Mil. Surgeon* 88: 1-24, 1941.
16. Keeley, J. L., Gibson, J., and Pijoan, M.: The Effect of Thermal Trauma on Blood Volume, Serum Protein and Certain Blood Electrolytes: An Experimental Study of the Effect of Burns, *SURGERY* 5: 572-593, 1939.
17. Schievers, J.: Le volume sanguin après brûlure étendue, *Arch. internat. de pharmacodyn. et de therap.* 52: 452-470, 1936.
18. Marino, Edmund R.: Personal communication to authors on cases observed at Queens General Hospital, and Mary Immaculate Hospital, Jamaica, N. Y.



# LEONTIASIS OSSEA COMPLICATED BY MARJOLIN'S ULCER

## OBSERVATION OF A CASE FOR TWELVE YEARS

RAY E. BURGER, M.D.,\* WELCH, W. VA., AND EDWIN P. LEHMAN, M.D.  
CHARLOTTESVILLE, VA.

(From the Department of Surgery and Gynecology, University of Virginia School of Medicine, Charlottesville, Va.)

VIRCHOW,\* in 1896, applied an old term, leontiasis, which had been used to designate nodular changes in the soft parts of the face of the leper, to cases presenting hyperostosis of the skull, adding the adjective, ossea. The term leontiasis ossea is descriptive of appearance, not of pathology.<sup>1</sup> Most early reports of the disease are on museum specimens, about which clinical data are meager. The first of these was in 1700 by Malpighi in the *Opéra Posthuma*. The present paper reports an instance of leontiasis ossea, seen first in 1930 and last in 1942, complicated by epidermoid carcinoma arising in a buccal fistula of seventeen years' duration.

Clinically, leontiasis ossea is characterized by slowly developing bony deformity of the face usually beginning in early life. There need be no other symptoms and signs unless the bony overgrowth impinges on the air passages of the face or upon various cranial nerves, in which case corresponding symptom complexes will develop. The syndromes resulting from encroachment on these structures bear the general name of craniostenosis.

In addition to infections around the nose, sinuses, and teeth, toxins, syphilis, trauma, and endocrine dysfunction have been proposed as etiologic agents. The malady has been compared with acromegaly and with Paget's disease. In leontiasis ossea the pathologic process is limited to the bones, whereas in acromegaly, both soft and osseous tissues are involved. Paget's disease occurs at an advanced age and is seldom localized to the head. Boyd,<sup>1</sup> however, has stated that leontiasis ossea and Paget's osteitis deformans are expressions of the same disease.

Elder includes leontiasis ossea among the fibro-osseous tumors of the skull and facial bones under the general term of diffuse osteomas. He regards them as true benign tumors, but admits the possibility that infection and trauma may act as irritative factors to initiate the process. The characteristic changes are the replacement of the bone marrow by fibrous tissue and, later, an excessive formation of new bone in this fibrous tissue.

\*Grace Hospital.

Received for publication, May 12, 1944.

In 1923. Lawford Knaggs<sup>3</sup> collected thirty-four cases, and reviewed the subject in detail. He divided the disease into cases of chronic periostitis, spreading slowly from bone to bone, to which the title of "creeping periostitis of the bones of the face and skull" was given, and cases of "diffuse osteitis of the bones of the face and skull." The periostitic form has its origin in the nasal fossae or sinuses, with large deposits of new subperiosteal bone as the inflammatory process creeps from bone to bone. The osteitic form was divided into (a) general, (b) circumscribed, or (c) local. The inflammatory changes were considered to be in the medullary portions of the bones. Knaggs believed the latter variety to be osteitis fibrosa affecting the cranial and facial bones. This opinion was expressed before the relationship between hyperparathyroidism and osteitis fibrosa cystica was understood and is, therefore, the result of clinical and pathologic observation only.

The disease usually affects the maxilla, malar bone, ethmoid and nasal bones, less frequently the sphenoid bone, parietal bones, and mandible, according to Mayer.<sup>5</sup> The involvement may be unilateral or bilateral. Ruppe<sup>7</sup> reported involvement of the first two cervical vertebrae.

X-rays reveal a general thickening of the bone. Mayer<sup>5</sup> listed the roentgen signs as follows: (1) There are considerable thickening and increased density of the bone, the thickening being intense and uniform. (2) The surfaces of the affected bone are entirely smooth and sharply defined. (3) The disease does not go beyond the anatomic margins of the bone or of a part of the bone if the latter has developed from more than one bony anlage.

Monti<sup>6</sup> has classified the disease as follows:

(1) *Leontiasis ossea facialis autonoma*: This constitutes the true type of the disease, affecting the young, represented by a slight productive periosteal change, beginning in the superior maxilla, limited in localization to the bones of the face and characterized by an extremely insidious progress. Histologically there is eburnation of the compact portion and of the spongy bone due to a disappearance of the osseous medulla. The nutrient vessels maintain their activity in nourishing the new osteoblasts and osteocytes. In this form of the disease there is a definite lack of a corresponding activity of bone absorption. (2) *Leontiasis ossea syphilitica*: This type differs from the preceding form in that it extends to involve the entire skull very early in the disease. Inasmuch as this form also affects the very young, symptoms of craniostenosis are frequent. (3) *Leontiasis ossea craniofacialis of osteodystrophia fibrosis*: More commonly this form, also occurring in the young, affects the interior of the skull, but it may also produce the characteristic external deformity of the disease. It differs essentially from the other forms in that the process begins in the osseous medulla, which becomes fibrous, while the lacunas become resorbed and the superficial compact zone becomes localized where the osteoclasts are present in large numbers. (4) *Leontiasis ossea of osteitis deformans*: In this type the deformity results from a rarifying osteitis and a process of condensation, which alternate. The latter is predominant and leads to an osseous hyperostosis, which is characterized by an intense irregularity of the disposition of the lamellar system.

Leontiasis ossea is rare and complete post-mortem studies are even rarer. All opinion in regard to the etiology of the disease and the nature of the pathologic process seems to be speculative, based on analogies with other bone disturbances. A review of the literature is profitable only in furnishing data on the clinical manifestations and the anatomic extent of this curious condition.

#### CASE REPORT

G. V. M. (Hist. No. 56693), a white man, aged 28 years, was admitted to the University of Virginia Hospital Dec. 8, 1930, with a history of having a very large lower jaw all of his life.

The family and past histories were irrelevant, except for a fracture of the left femur in 1920 repaired with a silver plate. There was a fracture of the same bone in 1929 treated by closed reduction.



Fig. 1—Photograph of the patient in 1930, revealing the large lower jaw.

The large jaw gave him no discomfort in early life, but progressively grew larger as he grew older. In April, 1925, he started having pain and swelling of the right side of the lower jaw, and began to expectorate pus and blood. This train of symptoms continued until August of the same year, when he entered another hospital where some dead bone was removed from the jaw, after which he improved. A salivary fistula remained on the right side.

He had no further trouble until five months before admission, when he began having pain and swelling of the left lower jaw, with expectoration of pus and blood. The symptoms continued, and as the aching pain became very severe, he came to this hospital for treatment.

Physical examination revealed a large, protruding lower jaw which extended downward about 9 cm. and was 11 cm. in width (Fig. 1). There was a long, broad scar on the right side with a salivary fistula present in this region (Fig. 2). The maxillae also appeared prominent. On inspecting the inside of the mouth, the floor was seen to be lengthened forward. Many teeth were missing; those

present were dirty and carious. There were several sinuses from the infected left mandible opening through the mucous membrane. The salivary fistula could be seen on the right side. The superior maxillae were massive and protruding (Fig. 2). The frontal sinuses could be transilluminated, the maxillary could not. The left leg was two inches shorter than the right. There was a ten-inch scar on the lateral side of the left thigh, and the femur was bowed laterally and anteriorly. Physical examination revealed no other relevant abnormalities.



Fig. 2—Photograph in 1930 showing massive enlargement of the superior maxillae and the opening of the buccal fistula. Note that the intermaxillary bone is apparently uninvolved. (See Fig. 7.)

X-rays revealed a large mass of osteoid tissue projecting from the lower jaw at its anterior portion. The maxillae also showed marked dense new bone formation projecting into the antra (Fig. 3). A diagnosis of leontiasis ossea was made. Roentgenograms of the calvarium (Fig. 4), shoulder girdle, pelvis, and long bones revealed no abnormalities except for the old healed fracture of the left femur which showed some deformity, and two small cystic areas in the lower end of the left radius.

Laboratory study revealed no abnormalities of the blood or urine. The blood Wassermann was negative. The blood calcium was 10.5 mg. per 100 c.c. The basal metabolic rate was plus 11.

While the patient was in the hospital, operation was performed on the left jaw at two different times, with removal of necrotic bone. Pathologic study of the tissue removed revealed only osteitis. He was discharged from the hospital Jan. 20, 1931, with the left jaw improved, and with instructions to return for a follow-up examination in several weeks.

The patient was readmitted to the hospital, April 23, 1931, having had considerable trouble with the left jaw during the previous month. Examination revealed considerable swelling of the left jaw with draining external sinuses, large sinuses opening into the mouth, and a large piece of necrotic bone presenting.

This was removed surgically. He was discharged from the hospital May 5, 1931, greatly improved.

He was not heard from again until six years later when he sent a letter to the hospital on an irrelevant subject. Following this occurrence, efforts were made to get him to return for follow-up study, but without success until June 18, 1942.



Fig. 3.—Roentgenogram in 1930 revealing the involvement of the superior maxillae and mandible.



Fig. 4.—Roentgenogram in 1930 showing no involvement at this time of the base of the skull or cervical vertebrae. Compare with Fig. 3.

During the eleven years since he was seen at this hospital, the jaw had grown progressively larger, and the salivary fistula had remained open. A considerable amount of osseous tissue had sloughed from the maxillae several years previously. He had received no treatment of the jaw in the interval except for dressings. He



Fig 5—Photograph in June, 1942, revealing the huge tumor of the right jaw, which was stony hard



Fig 6—Lateral view taken at the same time as Fig 5, showing ulceration and the buccal fistula in which later epidermoid carcinoma was demonstrated.

had had a third fracture of the left femur three years prior to admission, with closed reduction.

The tumor of the jaw had grown considerably larger in the past three years, with a great acceleration in growth during the past nine months. He had been able to work until then, but during the past nine months he had lost a great deal of weight and strength and had to go to bed one month previously.

Examination on admission, at the age of 39 years, revealed the patient to be anemic and malnourished, with moderate edema of the feet. There was a huge, round, solid tumor extending from the lower jaw downward, and resting on the chest (Fig 5). This tumor measured 32 by 22 by 22 cm. and presented large superficial ulcerations on both posterolateral surfaces. On the right side near the



Fig 7.—Photograph taken after operation, June, 1942 revealing the healing skin wound the openings into the antra and the persistent intermaxillary bone in which two teeth can be seen. Compare with Fig 2.

corner of the mouth was the buccal fistula, 9 cm. in diameter, the base filled with necrotic bone in granulation and the fistulous tract into the mouth lined with a firm tissue that it to be old granulation tissue (Fig. 6). The lower lip was pulled forward and downward and the floor of the mouth lengthened forward. The alveolar ridge appeared to be about 6 cm. in horizontal thickness and was continuous with the tumor mass. The patient could not close his mouth. Where the maxillary processes had sloughed there was a smooth mucosa lined communication between the cavity of the mouth and the antra and nose (Fig 7). The patient kept wads of tissue paper tucked in these openings. The only remaining

portion of the upper jaw was the intermaxillary process in which there were two carious teeth.

X-rays revealed a tremendous increase in the size of the sclerotic bone tumor of the mandible (Fig. 8), and some sclerotic bone involvement of the base of the skull and upper cervical vertebrae (Figs. 9 and 10). The large dense areas in the maxillae were no longer present. X-rays of the pelvis, lower spine, and long bones revealed no abnormalities except for the deformed left femur. The cystic areas in the lower end of the left radius were no longer evident. The chest roentgenogram was negative.

Laboratory study revealed a secondary anemia. The hemoglobin was 27 per cent (Dare), the red cell count 2,240,000, and the white cell count 37,000. The urine was negative. The blood calcium was 7.1 mg. per 100 c.c., the blood phosphorus 2.8 mg. per 100 c.c., and the blood phosphatase 7 Bodansky units. The patient was given three whole blood transfusions, following which the hemoglobin was 71 per cent (Dare), and the red count 3,430,000.



Fig. 8.—Roentgenogram showing the sclerotic bone tumor of the lower jaw. Note absence of dense masses in superior maxillae seen in Figs. 3 and 4.

June 25,\* 1942, under pentothal sodium anesthesia, the tumor was resected with considerable difficulty. Skin flaps were fashioned anteriorly and posteriorly, the tumor freed from the soft tissue, the alveolus delimited by mucosal incisions, and the horizontal ramus of the mandible cut across on both sides, freeing the tumor. The distortion was great, and the structures in the floor of the mouth could not be identified. The attachments of the sublingual group of muscles were cut, so that the hyoid bone was left with little muscular support. A good deal of blood was lost during the rapid operative procedure, and the patient's respirations were irregular due to plugging of the airway with blood and distortion of the trachea from the tug of the tumor during manipulation. A blood transfusion





Fig. 9.—Postoperative roentgenogram revealing remaining disease in the mandible and sclerosis involving the base of the skull and the upper cervical vertebrae.



Fig. 10.—Anteroposterior postoperative roentgenogram to compare with Fig. 9.

was given during the latter part of the procedure. A tracheotomy was performed as soon as the tumor mass was removed. Breathing then became smooth, and the patient's condition good.

The floor of the mouth was closed by uniting the incision at the base of the tongue to the incision in the sulcus of the lower lip with a continuous catgut suture. The exposed bulbous ends of the mandible were rongeured away. The defects in the muscles above the hyoid were closed with catgut. After this the skin flaps were trimmed for a rough, loose fit. The edges were tacked together with widely spaced fine silk sutures over two strips of petrolatum gauze. A biopsy was taken from the indurated tissue near the buccal fistula.

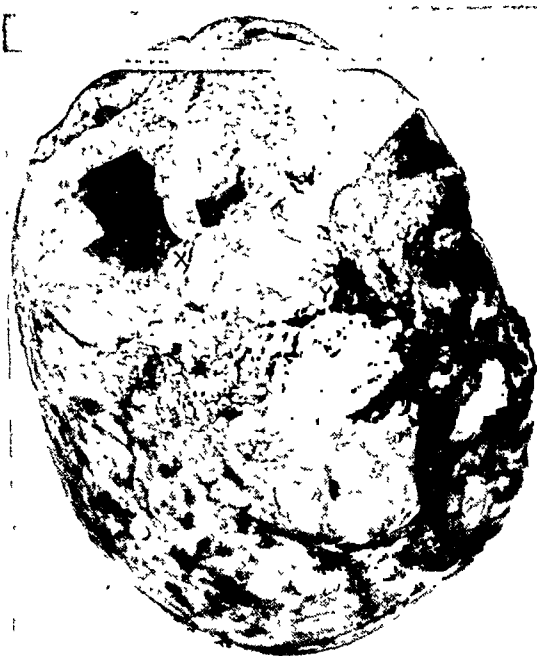


Fig. 11.—Photograph of the specimen from the superior-anterior aspect. Just lateral to X and Y respectively, the two cut ends of the mandible are seen with the enormously broadened alveolar process covered with mucosa stretching between them from X to Y. Below is the surface from which the anterior skin flap was removed; the cut edge of the remaining skin can just be seen at the lower border of the specimen. Epidermoid carcinoma was found in the tissue to the left of X.

Pathologic examination revealed a huge, ovoid, stony, hard tumor measuring 33 by 21 cm. and weighing 6,035 Gm. The tumor was covered mostly by skin except for the anterior aspect which represented the field of surgical operation (Fig. 11). On this surface were seen the cut rami and the intervening segment of the mandible from which the tumor obviously arose. A fistula partially lined with epithelium connected the superior aspect of the specimen with a large irregular area of ulceration about 8 cm. in diameter situated on the right antero-lateral aspect of the tumor just below the line of excision. The lining of the distal 2 or 3 cm. of this tract as well as the contiguous margin of ulcerated skin was much thickened and roughened and covered with purulent exudate which escaped abundantly from the surface of necrotic bone lying in the base of the large ulcer. The posterior aspect of the tumor, which had long rested upon the anterior chest wall, showed an irregular area of skin necrosis, obviously the result of pressure.

On section the entire tumor was found to be composed of calcified material resembling cancellous bone with abundant pearly gray fibrous stroma. Many large areas of necrosis were seen. There was no evidence of the formation of bone marrow, such as might be expected in a benign proliferation of cancellous bone. The entire mass had the appearance of a benign bone tumor in which much necrosis had occurred.

The microscopic examination of sections from many parts of the tumor showed various stages of the process by which this tumor was apparently formed. They may be listed as follows: (1) Well-formed areas of osteoid tissue without calcium surrounded by marginal osteoblasts imbedded in very abundant and cellular fibrous stroma (Fig. 12); (2) calcification of such areas to form cancellous bone with reduction in size and number of osteoblasts and with an increase of collagen in the surrounding stroma which at this stage appears less cellular (Fig. 12); (3) increase



Fig. 12.—Photomicrograph showing osteoid areas both uncalcified and calcified. The diminution of the number of osteoblasts about the calcified areas should be noted.

in the amount of stroma which appears to compress and distort the lamellae of cancellous bone. The latter in this stage were denser and showed no osteoblasts (Fig. 13); (4) necrosis of bone with granular masses of calcium and small fragments of necrotic bone embedded in dense fibrous stroma; (5) necrosis of large areas which are infiltrated with leucocytes.

Sections of the buccal fistula and the adjacent ulceration reveal epidermoid carcinoma, grade 1 (Fig. 14).

*Diagnosis.*—Osteitis fibrosa of the mandible (leontiasis ossea) with buccal fistula showing epidermoid carcinoma, grade 1.\*

The patient did well postoperatively. He was fed through an inlying gastric tube at first, but this and the tracheotomy tube were removed after ten days, and he was able to take liquids and later soft diet. The wound gradually healed

\*We are indebted to Dr. J. R. Cash, Professor of Pathology, for the pathologic study.

with some puckering of the line of union and of the flap (Fig. 15). The lips could not be closed, probably from prolonged stretching of the musculature of the lower lip. He was discharged, July 15, 1942, with instructions to return in six weeks.

The patient returned Aug. 27, 1942, having gained considerable weight and strength. There were fungating recurrences of the epidermoid carcinoma, proved by biopsy, on the right side of the jaw and in the midline where a small ulcer

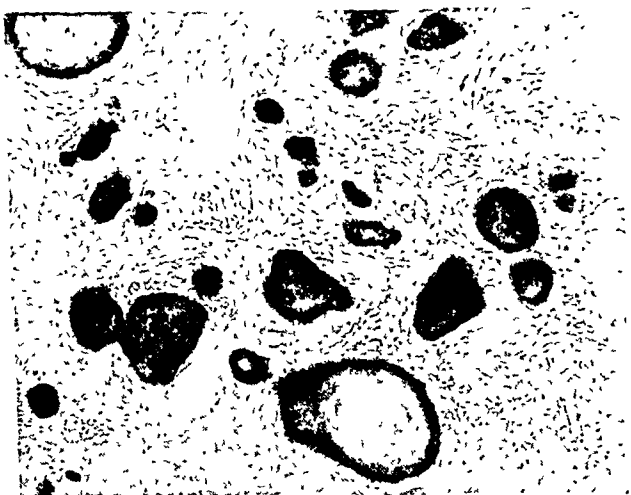


Fig. 13.—Photomicrograph showing an apparently later stage than Fig. 12. Note the condensation of the bone trabeculae, the complete disappearance of osteoblasts, and the increased relatively acellular stroma.



Fig. 14.—Photomicrograph showing areas of epidermoid carcinoma scattered among relatively mature bony trabeculae which may represent part of the original mandible.

was present (Fig. 16). An attempt at surgical excision was abandoned when the tumor was found to extend into the tissues beneath the tongue. The patient had taken the anesthetic poorly, and a second tracheotomy became necessary. The tumor was then treated with x-ray, being given a total of 4,000 r. through two lateral portals at 200 kilovolts. He was discharged again Sept. 28, 1942.

an early stage might modify the gradual spread of the lesion. Coppo is stated<sup>4</sup> to have reported a case of resection of the right superior maxilla for leontiasis ossea. The present case is also interesting on account of the enormous size of the jaw lesion which in itself caused complete disability. One of the earlier cases<sup>1</sup> (Case 17) shows a tumor of the jaw comparable to the present example. In the third place, the case illustrates the spread of the process into the upper cervical vertebrae, a phenomenon reported previously.<sup>7</sup> The limitation of the process to that portion of a bone arising in a single anlage as described by Mayer<sup>5</sup> is illustrated by the escape of the intermaxillary process although the superior maxilla on each side was involved to a marked degree.

Finally, the complicating epidermoid carcinoma which determined the outcome of the case is unique. This neoplasm is unquestionably of the same nature as Marjolin's ulcer occurring in chronic ulcer of the skin and in chronic sinuses. The incidence of epidermoid carcinoma in a buccal fistula has not been made the object of a search of the literature, but it must be excessively rare.

#### REFERENCES

1. Boyd, William: Textbook of Pathology, Philadelphia, 1938, Lea & Febiger, p. 998.
2. Eden, K. C.: The Benign Fibro-Osseous Tumours of the Skull and Facial Bones, Brit. J. Surg. 27: 323-350, 1939.
3. Knaggs, Lawford: Leontiasis Ossea, Brit. J. Surg. 11: 347-379, 1923.
4. Lederer, F. L.: Idiopathic Hyperostosis of the Skull, Arch. Otolaryng. 34: 88-98, 1941.
5. Mayer, E. G.: Ueber Röntgen- und klinische Befunde bei kranialen, bulbären Erkrankungen unklarer Ätiologie und ihre Wertung, Acta radiol. 9: 383-398, 1928.
6. Monti, A.: Quoted by Lederer<sup>4</sup> from Coppo, E., Sindrome nasale nelle leontiasi craniofaciale, Valsalva 14: 76-91, 1938.
7. Ruppe, C.: Leontiasis ossea et radiographie, Presse Méd. 37: 508, 1929.
8. Virchow, R.: Die Krankhaften Geschwulste, Berlin, 1864, A. Hirschwald, vol. 2, p. 23.

# A CASE OF A SPONTANEOUS GASTROJEJUNAL FISTULA EIGHT YEARS AFTER AN OPERATIVE GASTROJEJUNOSTOMY

LOUIS RENE KAUFMAN, M.D., F.A.C.S.,\* AND HELEN I. HEIMAN, M.D.,†  
NEW YORK, N. Y.

(From the Surgical Service, New York Medical College and Flower and Fifth Avenue Hospital, and the Metropolitan Hospital)

UNUSUAL problem cases are frequently encountered in a large city hospital service, and their reporting becomes an obligation. We are reporting a single case of unusual interest which we have not encountered at any other instance either in practice or in a survey of the literature. The case is that of a new spontaneous gastrojejunal fistula, following a posterior gastrojejunostomy performed eight years previously.

CASE REPORT—C. McL. was admitted to the Metropolitan Hospital April 1, 1943. The patient was a 70-year-old white woman, complaining of dysphagia, vomiting, and loss of ten pounds for the previous three months. She had had symptoms of dyspepsia and nausea since youth. Eight years previously, a posterior gastrojejunostomy had been performed for duodenal ulcer, and the patient was then comfortable and symptom free for the first time in her life until the onset of this illness three months prior to admission.

Physical examination showed a chronically ill, white woman with marked pallor and evidence of weight loss. There was a right rectus scar and medial to this very slight epigastric tenderness, but no abdominal masses were noted. Examination was, otherwise, negative.

X-ray and fluoroscopy revealed a normal esophagus, but the stomach was enlarged, and there was a five-hour residue; the gastrojejunal stoma was not visualized. Several gastric analyses showed high total acid up to 75, high free acid up to 48, high combined acid of 27, with occult blood in most specimens.

Gastroscope revealed a patchy, superficial gastritis with some adherent exudate and punctate hemorrhages. The rugae were atrophic. There was a pseudovalve of the stoma, but the opening was more than adequate, and the jejunum was easily and clearly seen. The many jejunal peristaltic waves indicated possible obstruction below the stoma. There were 2,000 cc. of gastric residue.

The patient was treated with gastric lavages, numerous transfusions, liver extract, and iron. Hemoglobin increased from 52 per cent to 70 per cent, and there was marked improvement both subjectively and objectively. After three weeks, exploratory laparotomy was undertaken with the view to doing a subtotal gastrectomy if this were possible.

At operation, the stomach was found greatly dilated. Easily separable adhesions bound the anterior surface to the round ligament and parietal peritoneum. About where one would expect the gastrojejunostomy to be found, an anastomosis was visualized, and sharp angulation of both proximal and distal jejunal loops noted. The apparent stoma was located in the transverse mesocolon just at the edge of the

\*Director of Surgery, Metropolitan Hospital, Professor of Surgery.

†Resident in Surgery, Metropolitan Hospital.

Received for publication, April 5, 1944.

colon, in the midst of a large inflammatory mass, about 11 by 4 by 7 cm. The anastomosis was taken down by dissecting the mass, first from the colon and mesocolon, and then from the stomach. The part of the jejunum attached to the mass was resected, and an end-to-end anastomosis of the jejunum was done.

The gastric wall surrounding the site of the anastomosis was inflamed and thickened for a radius of about 2 cm. That portion of the wall was resected. A finger was inserted into the stomach through this opening and exploration revealed that distal to it was a wide orifice into what was thought to be the duodenum. (However, autopsy later revealed that this orifice was the original gastrojejunostomy; the "anastomosis" which was let down was the spontaneous inflammatory gastrojejunostomy.) The defect of the stomach wall was completely closed, and the rent in the mesocolon was sutured. While the stomach was open, a Levin tube was guided well into the small intestine.

*Postoperative Course.*—The patient was given oxygen and several transfusions. The Levin tube was aspirated at intervals and large quantities of dark brown fluid were removed. Twenty-four hours post-operatively, the patient suddenly went into shock and expired.

*Autopsy Report.*—The mucosa of the stomach presented some reddening and no ulceration. Rugae were not prominent. The region of the pylorus showed complete obstruction with an area of white scar tissue which occluded the opening into the duodenum. An apparently well-functioning anastomosis between the jejunum and posterior gastric surface was present. Proximal to this anastomosis was a sutured defect of the posterior gastric wall. In the descending loop of the jejunum, distal to the gastrojejunostomy, was an end-to-end anastomosis surrounded by a certain amount of edema. The mesocolon was scarred, and the transverse colon was thickened.

#### DISCUSSION

At operation, what was thought to be the old gastrojejunostomy with a marginal ulcer was resected. Since it was felt that there was a patent pylorus and duodenum, no new jejunostomy was performed.

At autopsy, it was shown that what we had thought to be a patent pylorus was a well-functioning, eight-year-old gastrojejunostomy. The stoma was located almost in the pyloric antrum at the greater curvature with a short loop of jejunum about 14 cm. from the ligament of Treitz. The area resected was a spontaneous gastrojejunostomy, about 8 cm. proximal to the artificial one (proximal in the stomach, but distal in the jejunum; see Fig. 1). The pylorus had apparently not been patent for the past eight years.

The most frequently discussed complication following gastrojejunostomy is gastrojejunal ulcer. Fistulas, when present, generally involve the colon. Lahey and Jordan,<sup>1</sup> in analyzing these fistulas, do not mention the formation of a spontaneous communication between the stomach and jejunum, the simple gastrojejunal type, but discuss only gastrocolic, jejuno-colic, and gastrojejuno-colic fistulas. The reported incidence of ulceration has varied from 3 per cent to 34 per cent.<sup>2,3</sup> The site is usually at the anastomosis or in the efferent jejunal loop, 1 to 10 cm. distal to the stoma. Only rarely is the afferent loop affected. It is generally accepted that ulcers are produced more easily in those sites farther away from the segment which has adapted itself to receive acids. Operative technique has little bearing on the production of

ulcers opposite or some distance from the stoma,<sup>4</sup> but, as in our case, the high acid is obviously an important factor in causing the recurrent ulcer.

There is a higher incidence of jejunal ulcer in cases in which the pylorus is closed off. According to Alvarez,<sup>5</sup> "Anything that interferes with the passage of duodenal contents over the jejunal mucosa around the stoma is likely to leave this region unprotected from the corrosive effects of gastric juice and, therefore, subject to ulceration. Closure of the pylorus probably interferes with the maintenance of a good downward current in the duodenum, and the absence of food and gastric juice in the duodenum lessens the outflow of the protective bile and pancreatic juice." This is confirmed by Lahey,<sup>6</sup> who feels that pyloric obstruction is a predisposing factor for gastrojejunal ulcer since the highly acid gastric contents are dumped into the jejunum and cannot mix with the regurgitant alkaline contents.

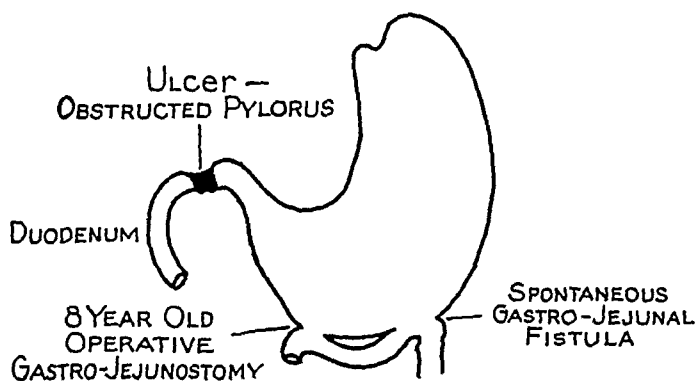


Fig. 1.

Most cases of gastrojejunal ulcer show a clinical course similar to that in peptic ulcer. Such symptomatology was absent in our patient who had been comfortable for eight years and began to complain only three months previously when signs of obstruction appeared. Hoag and Saunders<sup>7</sup> list the causes of obstruction following gastrojejunostomy in the following manner:

1. Improperly placed stoma
2. A stoma so small or narrow of attachment that it produces acute angulation of the jejunum
3. A proximal loop of excess length or so short as to obstruct with changing position of the stomach
4. A rigid and short mesocolon which fails to stretch on filling of the stoma
5. Inadequate fixation of the stoma to the mesocolon and internal hernia
6. Adhesions about the stoma
7. Pressure of the middle colic artery



8. Marginal or jejunal ulcers at or near the stoma
9. Adhesions distal to the anastomosis
10. Hypoproteinemia

Only the last three causes, 8, 9, and 10, were present in our case.

In view of the marked gastritis in this case, the question has been raised as to whether the spontaneous gastrojejunal fistula may have followed a perforated gastric ulcer. This is an unlikely sequence of events. Such an ulcer on the posterior stomach wall is not usual, although one was reported by Edwards<sup>6</sup> on the lesser curvature. It is more probable that the gastritis was secondary to the obstruction.

The failure of the gastrosopic examination to visualize the secondary opening bears mention, particularly in view of the accurate description of the stoma with the peristaltic jejunal waves indicating obstruction. The patchy exudate on the mucosa probably obscured the other opening.

In the evaluation of the pathology present in this case, one may assume two hypotheses to explain the origin of the new spontaneous gastrojejuno-stomy. The record indicates that eight years after the original gastrojejuno-stomy the patient developed an acute condition at least suggestive of an ulcer. This ulcer may have originated in the greater curvature of the stomach as a new gastric ulcer—an unlikely occurrence as noted. On the other hand, the ulcer may have developed as a jejunal ulcer, about 8 cm. distal to the original gastrojejuno-stomy in a location where the impact of the acid chyme would be most likely to produce ulceration of the jejunal mucosa. As the ulceration progressed to and through the serosa, inflammatory reaction might readily fix this distal segment of the original loop to the greater curvature as well as to the gastrocolic omentum since it was in close proximity to both. Further progression of the lesion might, therefore, readily result in perforation with a spontaneous gastrojejunal fistula. The marked inflammatory reaction which we noted at the time of operation lends further support to this hypothesis.

#### SUMMARY

A case is presented of a spontaneous gastrojejunal fistula occurring eight years after a posterior gastrojejuno-stomy and causing obstruction. Gastrojejunal ulcer with its complications is briefly discussed.

#### REFERENCES

1. Lahey, F., and Jordan, S. M.: *Ann. Surg.* 87: 243, 1928.
2. Walters, W., and Clagett, O. J.: *Am. J. Surg.* 46: 83, 1939.
3. Lewisohn, R.: *S. Clin. North America* 16: 805, 1936.
4. Ginzburg, M. D., and Mage, S.: *Surg., Gynec. & Obst.* 67: 788, 1938.
5. Alvarez, W. C., quoted by Neuwelt, et al.: *Am. J. Digest. Dis.* 8: 310, 1940.
6. Lahey, F.: *S. Clin. North America* 20: 767, 1940.
7. Hoag, C. L., and Saunders, J. B.: *Arch. Surg.* 42: 259, 1941.
8. Edwards, H. C.: *Lancet* 2: 1127, 1934.

## PANTOPAQUE

### NOTES ON ABSORPTION FOLLOWING MYELOGRAPHY

CAPTAIN GEORGE M. WYATT, AND LIEUTENANT COLONEL ROY G. SPURLING  
MEDICAL CORPS, ARMY OF THE UNITED STATES

*(From the Sections of Roentgenology and Neurosurgery, Walter Reed General Hospital, Washington, D. C.)*

PANTOPAQUE has replaced Lipiodol and the gases as the contrast medium for myelography in the Army Medical Corps. The chief reason for the preference to lipiodol is that Pantopaque is absorbed instead of remaining as a persistent foreign substance in the subarachnoid space.<sup>1-3</sup> Experience has shown it to be nontoxic and no more irritating than lipiodol, and its sharp radiographic contrast and consequent clear delineation of pathologic anatomy affords a definite superiority over the gases as does lipiodol. In contrast to lipiodol, pantopaque is more fluid than viscous and therefore fills out the smaller spaces such as the dural nerve sheaths. It also is more easily removed following examination.

The chief advantage of pantopaque, however, lies in its absorbability and it is the purpose of this paper to discuss this absorption as observed roentgenologically.

Observations at the Walter Reed General Hospital at intervals of a few weeks or months following injection of pantopaque suggested that absorption might not be so rapid in all patients as it was previously thought to be.<sup>1-3</sup> Accordingly, follow-up x-ray pictures were obtained for six patients in whom the removal of pantopaque had been incomplete. These roentgenograms included the skull and entire spine and sacrum to exclude the possibility of migration of the contrast material. The patients were selected from the first group in which pantopaque was used at the Walter Reed General Hospital, the sole bases of selection being incomplete removal and availability for follow-up study. All of these patients had ruptured intervertebral discs removed surgically but in no instance was the dura entered or any attempt at removal of the residual pantopaque made during the operation.

Amounts of residual pantopaque were estimated on the basis of the size and number of the collections shown on the x-ray pictures. Obviously such estimation is crude and the figures arrived at will vary with the individual observer. There was, however, no doubt that the material was being absorbed at a significant rate of speed (Figs. 1 and 2).

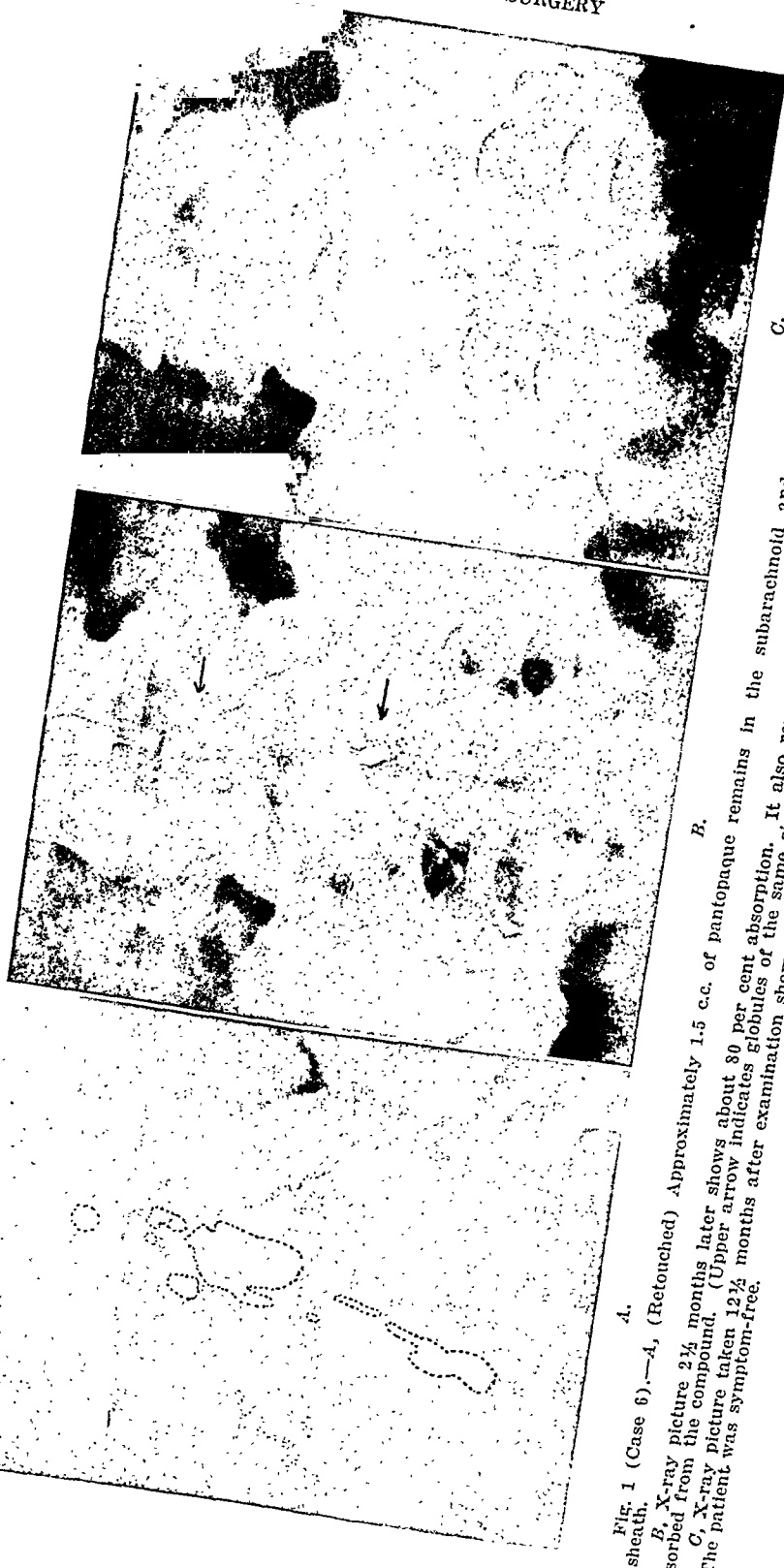


Fig. 1 (Case 6).—A, (Retouched)

B, X-ray picture 2 1/4 months later shows about 80 per cent absorption.

C, X-ray picture taken 12 1/2 months after examination shows about 90 per cent absorption. It also represents the only instance in which iodine was seen to be absorbed from the compound. (Upper arrow indicates globules of the same size but less density than those indicated by lower arrow.)

C.

The patient was symptom-free. It also represents the only instance in which iodine was seen to be absorbed from the compound. (Upper arrow indicates globules of the same size but less density than those indicated by lower arrow.)

The patient was symptom-free. It also represents the only instance in which iodine was seen to be absorbed from the compound. (Upper arrow indicates globules of the same size but less density than those indicated by lower arrow.)



Fig. 2 (Case 3).—A, Approximately 0.5 c.c. of pantopaque remains in the subarachnoid space.  
 B, Roentgenogram 1½ months later shows about 75 per cent absorption.  
 C, Roentgenogram 14 months after examination shows about 95 per cent absorption. The droplets are fixed in the same position as in B.

Estimates of residual amounts and percentage absorption were arrived at separately by us. An approximate average of these estimates is presented in Table I.

TABLE I  
ESTIMATED ABSORPTION OF RESIDUAL PANTOPAQUE

CASE NO.	AMOUNT INJECTED AT EXAMINATION (C.C.)	AMOUNT NOT REMOVED AT EXAMINATION (C.C.)	TIME INTERVAL AFTER EXAMINATION (MO.)	PERCENTAGE ABSORPTION
1	3.5	0.1	9	70
2	3.5	0.2	1 $\frac{1}{2}$	None perceptible
			6 $\frac{1}{2}$	
			15	
3	3.5	0.5	1 $\frac{1}{2}$	50
			14	80
4	3.5	1.0	13	75
5	3.5	1.5	15	95
6	3.5	1.5	2 $\frac{1}{2}$	90
			12 $\frac{1}{2}$	80
				90

As judged by the x-ray shadows there was a definite decrease in the amount of residual pantopaque in all cases. The size and density of the remaining droplets showed that this decrease was due to absorption of the entire compounds rather than of iodine from the compound. In several instances minute residual droplets were as opaque to the x-ray as larger droplets seen immediately following incomplete removal. If the decrease in density seen by x-ray were due to the absorption of iodine from the compound rather than absorption of the total mass, the remaining small collections would lose their radiopacity. In only one instance was a relative decrease in density of residual droplets observed (Fig. 1). The general tendency was toward a progressive increase in density with decrease in the total amount remaining.

Absorption was usually most rapid during the first few months following examination (Figs. 1 and 2). Following this initial absorption, the small remaining droplets were absorbed at a relatively slower rate. Slow absorption of minute amounts was also demonstrated by Case 6 (Table I and Fig. 3). In no instance was absorption complete during the period of observation, although the continued change in all instances warrants the assumption that complete absorption will eventually take place.\*

The variations in the rate of absorption and in the density of the residual droplets may be due to the nature of the contrast medium which is a mixture of isomers. Some of the isomers may vary slightly in absorbability.<sup>3, 4</sup>

Another factor which may be responsible for the faster absorption of larger amounts of pantopaque is the emulsifying action of body motion on the larger collection of 0.5 c.c. upward. Such emulsifying action is best observed during cervical myelography during which the contrast medium flows the entire length of the spine (Fig. 3). The surface area

\*Since this article was submitted for publication, one of us (G. M. W.) has observed complete absorption of approximately 1 $\frac{1}{2}$  c.c. of pantopaque in a period of eleven months.

presented by the small particles is much greater in relation to the total mass considered as a single spheroid than is the surface area presented by a few small droplets. When only a few small droplets remain the tendency is toward coalescence rather than breaking up with body motion.

As previously stated, the entire subarachnoid space was surveyed. The contrast medium was observed to flow as high as the first lumbar vertebra but none of the roentgenograms revealed any pantopaque in the skull, cervical spine, or thoracic spine. The only explanation for the lack of migration is that the patients did not assume the head-down

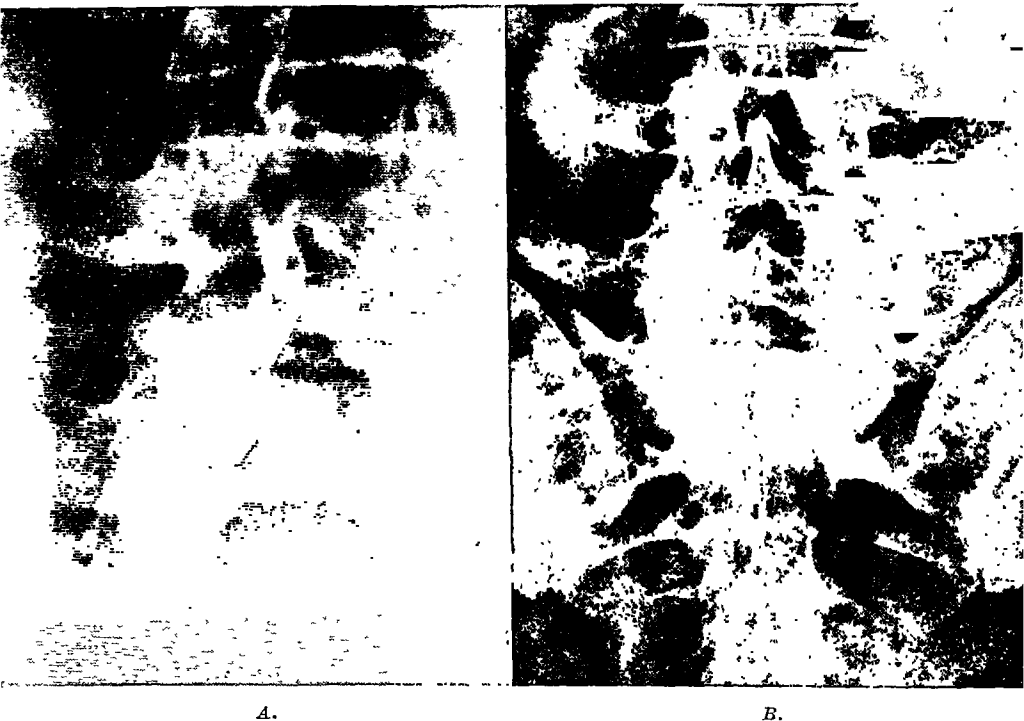


Fig. 3 (Case 1).—A, A minute quantity (estimated as 0.1 c.c.) of pantopaque remains in the subarachnoid space.

B, Roentgenogram 9 months later shows only about 70 per cent absorption. The small remaining droplets are relatively as dense or denser than the original compound.

position during the first few weeks following examination. After a month or two, the material becomes fixed in position. This fixation indicates some tissue reaction to residual pantopaque. None of the patients, however, had any symptoms referable to the residual material, even though in one instance some pantopaque had been injected subdurally and remained in a nerve sheath (Fig. 2).

#### CONCLUSIONS

1. Pantopaque is absorbed from the subarachnoid and subdural spaces of the human body.

2. The most rapid absorption occurred during the first few months following injection.

3. Although absorption was not complete during the periods of observation, the continued absorption in all instances warrants the assumption that complete absorption will eventually take place.

4. No toxic reactions were observed.

#### REFERENCES

1. Strain, Wm. H., Plati, John T., and Warren, Stafford, L.: Iodinated Organic Compounds as Contrast Media for Radiographic Diagnoses. I. Iodinated Aracyl Esters, *J. Am. Chem. Soc.* 64: 1436-1440, 1942.
2. Spurling, R. G., and Thompson, T. C.: Notes on the Diagnosis of Herniated Nucleus Pulposus in the Lower Lumbar Region, *Army M. Bull.* 68: 142-154, 1943.
3. Spurling, R. G., and Thompson, T. C.: Notes on the Diagnosis of Herniated Nucleus Pulposus in the Lower Lumbar Region, *SURGERY* 15: 387-401, 1944.
4. Strain, Wm. H.: Personal communication.

# Editorial

---

## The Obligations of an Internist to a General Surgeon

**A**N INTERNIST has been defined as a man who is totally unable to answer either yes or no to any question. The definition was made in jest but there is much truth in it. If there is such a thing as a typical internist, he is a sedentary individual, curious, skeptical, reflective. He is accustomed to look at the patient as a unit rather than as a collection of separate organs and, if he has had the fundamental scientific training he should have had, he is eager to distinguish between a fact and someone's opinion. Although often powerless to suggest an alternative procedure, he regards every operation as an exercise in violent therapeutics and a confession of failure to cure. He is, however, humble before the complexities of modern surgical technique. His fees are not such as to command general admiration.

The surgeon, on the other hand, is a man of action. He lives in an exhilarating world of knives, blood, and groans. His tempo is of necessity rapid. He is inclined to look at his less kinetic colleague with an air of puzzled condescension but may, in a relaxed moment, admit that the medical man is occasionally able to assist uncomfortable dowagers in the selection of a cathartic. Accustomed to legerdemain and quick results, he is apt to regard the diagnosis and treatment of a headache, for example, as a trivial matter, forgetting that the internist may require hours of probing before discovering that what the patient needs is not a new pair of glasses but a different mother-in-law. The surgeon and the internist are workers in the same vineyard, but their points of view are inevitably different.

Of those patients who come to any clinic for help there is a certain small percentage who present definite and well-demarked problems—a broken arm, a decompensated heart, a gravid uterus, for example. Of these the internist will claim his share and do what he can. Over and above these, however, is a larger number with ill-defined complaints who tax the resources of the entire staff. These are the ones who are commonly x-rayed from head to toe, whose fluids and excrements are examined with great skill, into whose every orifice electric lights are inserted—to no avail! The standard reaction on the part of the medical attendant then is that of anger. The patient is automatically regarded as an imposter who has no right to his symptoms and his visit to the clinic is looked upon as a nuisance and an intrusion. Actually, of course, these are perhaps the sickest people we see. It may be argued that they are merely suffering from such elemental emotions as grief, frustration,



inadequacy, fear, or sorrow, that their problems are therefore non-medical, and that the clinic is not required to help them. If this is so, we are amateur physicians indeed.

W. R. Houston has frequently and eloquently pointed out that sickness of any sort carries with it a curious and sometimes irresistible demand for action. There is nothing to which a sick man will not submit himself—he is gladly purged, puked, bled, transfused, sweated, infused, cut, frozen, heated, and shocked and he will swallow literally anything. It is seldom that the consequences of these actions are considered, for it is action itself that is demanded. Even the most normal of us howl and gyrate when thrust suddenly into pain; these actions serve no useful purpose whatever, but somehow they seem to bring relief.

And so these people come to us in their distress demanding both action and relief. This demand comes not only from the patient but from the family as well. One can never enter a sickroom without being immediately aware of immense forces at work. The urge to violence is often so compelling that it requires great courage to follow the wiser course and do nothing. Certainly it is a commonplace experience for patients to complain that we have found nothing for which to operate upon them, and it is no consolation to these people to be told that their roentgenograms and blood tests are negative. It is another curious fact that no one minds being told that he has something wrong with one or more of his organs, but he bitterly resents the implication that the trouble lies within himself. A heart that is failing a little, a sluggish liver, a pair of weak lungs—these are cherished and respected ailments—but a personality defect is accepted with the greatest reluctance.

In dealing, as it must, with individuals whose primary difficulty is emotional, a clinic finds itself in a peculiarly dangerous situation because a certain percentage of these patients will inevitably present some physical abnormality which, in a more stable host, would be a legitimate surgical target. The diagnosis of anxiety state, chronic reactive depression, or conversion hysteria is not made by exclusion, however, and it would be a major error to assume that an elderly housewife could not have a psychogenic backache and a fibroid tumor as well. The surgeon often accuses the internist of complacency and ignorance when he chooses to ignore a uterus which is not quite perpendicular, or a solitary gallstone, or a pair of tonsils from which a fluid of unknown composition can be expressed. There are certain people, however, who demand violence; the surgeon enjoys removing organs and one function of the internist is to see that these two never meet.

—*Thomas Findley, M.D.*  
New Orleans, La.

# Recent Advances in Surgery

---

CONDUCTED BY ALFRED BLALOCK, M.D.

---

## AN ANALYSIS OF THE MORE IMPORTANT ORTHOPEDIC INFORMATION

PRESENTED AT

THE TWELVE REGIONAL FRACTURE ORTHOPEDIC CONFERENCES OF THE  
ARMY AIR FORCES

SPONSORED BY

THE AIR SURGEON

OCT. 18 TO NOV. 27, 1943

LIEUTENANT COLONEL ALFRED R. SHANDS, JR.,\* MEDICAL CORPS,  
ARMY OF THE UNITED STATES

### INTRODUCTION

DURING the fall of 1943 the air surgeon, through his Medical Services Division, conducted twelve two-day regional fracture orthopedic conferences within the limits of the continental United States, at which 196 papers were presented. As orthopedic consultant to the Army Air Forces, I attended all conferences and made written notes on the information presented in both the papers and the discussions. The purpose of this publication is to analyze the more important orthopedic information presented at these meetings and to bring this to the attention of medical officers and physicians responsible for the treatment of orthopedic conditions and fractures in the Armed Forces and in civil practice. One hundred nineteen papers were submitted after the conferences. These have been carefully reviewed for this publication. Many of them will be published later.

In analyzing this considerable volume of data and selecting material for presentation, I have laid especial emphasis upon the following: (1) new and original ideas appearing worthy of consideration, (2) old ideas on pertinent subjects presented in an original and instructive manner, (3) opinions on controversial subjects, and (4) statistics on incidence, operations, and end results. An attempt has been made to report accurately and to interpret clearly this information as derived from both the papers and the discussions. I have interpolated comments where they seem indicated but have tried not to confuse the reader with too much of my own opinion.

In this analysis the names of medical officers and physicians from whom the information has come, with the exception of those of a few

---

\*Consultant in Orthopedic Surgery to the Army Air Forces and Chief of the Surgical Branch of the Professional Division, office of the Air Surgeon.

prominent civilian physicians, have purposely been omitted; upon request, however, I will supply the source of all information.

The papers on Convalescent Rehabilitation, Physical Therapy, Burns, Cranial Injuries and Anesthesia are not included in this analysis. There were many excellent contributions in this group.

An excellent paper on Bone Metabolism was presented, in which the delay in fracture healing at high altitudes was described. This paper, which contains many entirely new ideas, has not been included in the present analysis because it should be published first by its authors as an independent contribution. Also, such presentations as Historical Notes on Military Orthopedics and Psychiatry in Orthopedic Surgery will be published as complete papers.

Before each meeting, a list of suggested titles and speakers was sent to the orthopedic surgeon who was to serve as host and he was directed to organize his own program. The twelve final programs included 196 papers; their subjects, divided into suggested and miscellaneous titles, were as follows:

#### ANALYSIS OF THE SUBJECTS OF THE SCIENTIFIC REPORTS

##### *A. Suggested Titles*

	NO. OF PAPERS
1. Splinting and Transportation of Fractures	12
2. Fractures and Dislocations of Hand and Wrist	12
3. Fractures and Dislocations of Forearm, Elbow, and Arm	11
4. Fractures and Dislocations of Shoulder	12
5. Fractures and Dislocations of Hip, Thigh, and Knee	13
6. Fractures and Dislocations of Leg and Ankle	10
7. Fractures and Dislocations of Foot and Toes	12
8. Fractures and Dislocations of Spine and Pelvis	10
9. Compound Fractures	10
10. Conditions Involving the Back	11
11. Conditions Involving the Knee	11
12. Conditions Involving the Foot	12
13. Convalescent Rehabilitation	12
14. Physical Therapy	7
15. Burns	12

##### *B. Miscellaneous Titles*

16. Amputations	1
17. Anesthesia	3
18. Ankle Sprains	1
19. Aseptic Necrosis	1
20. Aviation Medicine	1
21. Bone Graft Surgery	1
22. Bone Metabolism	1
23. Casualties in Italian Prisoners of War	1
24. Cerebral Injuries and Skull Fractures	5
25. Complications of Fractures	1
26. Early Laminectomy for Spinal Cord Injuries	1
27. External Skeletal Fixation (The Stader Method)	1
28. Historical Notes on Military Orthopedics	1
29. Infections of the Hand	1
30. Intravenous Morphine	1
31. Jaw Fractures	2
32. Management of the Sick Orthopedic Patient	1
33. Orthopedic Conditions and "64" Examination for Flying	1
34. Penicillin	2
35. Protrusions of the Intervertebral Disc	1
36. Psychiatry and Orthopedic Surgery	1
<i>Total</i>	<u>196</u>

Of the 196 essayists, 128 were from the Army Air Forces, 43 from the Army Service Forces, 24 from civilian practice, and 1 from the Navy. There was an average of 16 papers per conference.

At these twelve conferences there was an average attendance of 122 officers and civilian physicians. Of the 1,460 total attendance, 1,194 were from the Army Air Forces, 145 from the Army Service Forces, 96 from civilian practice, and 25 from the Navy.

Attending the conferences were representatives of 304 Army and Navy hospitals, as follows: 228 station hospitals of the Army Air Forces, 31 general and 39 station hospitals of the Army Service Forces, and 6 hospitals of the Navy.

In conclusion to these introductory remarks, I wish to express my appreciation and thanks to those in the twelve conference hospitals who made each meeting possible; to those presenting the papers and participating in the discussions, who contributed the wealth of scientific information which forms the basis of this report; to Colonel Leonard T. Peterson of the Surgeon General's Office, and Dr. R. Beverly Raney of the Duke University School of Medicine, who have so kindly read and criticized this report; and finally to the Air Surgeon, Major General David N. W. Grant, to the Chief of the Medical Services Division of the Air Surgeon's Office, Colonel William P. Holbrook, and to those others in the Air Surgeon's Office who, by their help and advice, have added so much to the success of these meetings. It is to be hoped that the conferences were of value to those attending and that this review and analysis may be of assistance to those physicians who are treating orthopedic conditions and fractures in the Armed Forces and in civilian practice.

#### PART I. FRACTURES AND DISLOCATIONS ABOUT THE SHOULDER

The group of fractures and dislocations about the shoulder constitutes approximately 5 per cent of the total. A very large number of injuries of the acromioclavicular joint have been reported and also a large number of recurrent dislocations of the shoulder.

##### *1. The Clavicle*

The importance of accurate reduction of fractures of the clavicle was repeatedly emphasized in all conferences. It was stated that the irregular bony surfaces of a malunion make it impossible for a soldier to carry a gun or pack on his injured shoulder with comfort. One officer from a general hospital had observed twelve malunited fractures, and an officer from a station hospital had operated on two malunions. Non-union of the clavicle is extremely rare; however, six cases were reported from one general hospital.

It was pointed out by two officers that for the extensively comminuted and displaced fracture whose reduction cannot be maintained by ambulatory splints, recumbency and lateral traction to the upper arm with

the shoulder abducted is an effective form of treatment. Four excellent results were reported with this method of treatment.

The figure-of-eight dressing, usually made of plaster, is apparently more popular than the T splint; I believe, however, that the T splint is the more effective and better dressing. The immobilization period recommended was from three to six weeks. At one conference there was a favorable discussion of the Kirk-Peterson splint for fractures of the clavicle.

(*Comment.*—Fractures of the clavicle frequently unite with malunion, but in civil practice this seldom results in disability. In the Army, however, the rough edges and bony spicules of a malunion may be a constant source of annoyance and pain, because of the rubbing of the strap of a heavy knapsack or gun. Hence, accuracy of reduction is important and every effort should be made to obtain it. Lateral traction on the upper arm in recumbency may be the treatment of choice for extensively comminuted or displaced fractures.)

## 2. Sternoclavicular Dislocation

Sternoclavicular dislocations were observed infrequently. One officer reported the insertion of short Kirschner wires through the sternum and into the clavicle to maintain reduction. A fascial repair operation for chronic dislocations was mentioned at one conference.

(*Comment.*—The use of Kirschner wires across this joint may maintain reduction but is accompanied by some risk and should be undertaken only in the exceptional case. When wires are used, every precaution should be taken to prevent their inward migration, a complication which can readily occur.)

## 3. Acromioclavicular Dislocation

Acromioclavicular dislocation was discussed frequently. The common occurrence of this injury and its generally poor end result indicate that it is a real problem. Especially is this true when the coracoclavicular ligaments are ruptured and the dislocation is complete.

In many conferences there was a discussion of the use of a plaster dressing to aid in maintaining reduction of this dislocation. The dressing was applied usually in the form of a hanging body cast. One officer recommended adding to the cast a shelf for support of the elbow and forearm, in order to prevent the upper extremity from hanging down at the shoulder. A three-inch elastic bandage, taken from a rubber bandage tourniquet, was incorporated in the cast by a second officer in such fashion that the weight of the cast acting through the bandage exerted a constant downward force on the outer end of the clavicle. One physician demonstrated a twelve-inch plaster girdle incorporating a wide cotton webbing strap over the outer end of the clavicle. Three

officers recommended that a plaster spica cast with the shoulder in 90 degrees of abduction be worn from six to nine weeks.

There were several reports of a circular dressing around the outer end of the clavicle and the olecranon, adhesive plaster or a two-inch webbing strap and buckles being used. Mention was made by one officer of 138 cases reported by Thorndike of Boston, in which the circular adhesive dressing was used with good results. Whether these dislocations were complete or incomplete was not stated.

There were three reports on immediate open operation for this dislocation with an attempt to suture the torn ligaments.

One officer was of the opinion that if after three weeks the joint was unstable, an open procedure was indicated. Two officers reported the insertion of Kirschner wires from the acromion into the clavicle to fix the joint. These wires crossed the joint line and were left in place from six to eight weeks. Three excellent results were reported. Another officer reported maintaining the reduction with a large caliber Kirschner wire or a small Steinmann pin placed through the outer end of the clavicle into the acromion but not crossing the joint line. This was supplemented by a circular adhesive dressing around the elbow and outer part of clavicle. The operation of tying the clavicle down to the coracoid process with wire or fascia lata was also recommended.

There were two reports on the Vargas operation (construction of a new coracoclavicular ligament by the use of a portion of the short head of the biceps). One officer reported seven successful results, a second officer one failure.

The Mumford operation for dislocation (excision of the outer end of the clavicle) was favorably reported at two conferences; however, at one conference a weak and painful shoulder following the operation was reported.

(*Comment.*—The evidence from these discussions of the many different methods of treatment certainly indicates that no single nonoperative or operative method is always satisfactory. From personal experience, I am of the opinion that if the dislocation is complete, indicating a total rupture of the coracoclavicular ligaments, some type of open fixation of the clavicle to the acromion, with a repair of torn ligaments when possible, is immediately indicated. My clinic has four satisfactory end results from inserting three Kirschner wires through the acromion into the clavicle across the acromioclavicular joint, care being taken to turn up the outer ends of these wires in order to prevent their inward migration. At the time of operation the torn superior acromioclavicular ligaments are repaired. The wires are left in for eight weeks.

Reports of good end results following the Vargas and Mumford operations are still too few to warrant complete approval of these operative procedures for use in military surgery.)

#### 4. *Dislocation of the Shoulder*

*a. Acute.*—In all of the conferences there was considerable discussion regarding the acute dislocation. The advisability as well as the necessity of using a general anesthetic for early reduction of the dislocation was frequently discussed. Five officers stated that they were using a general anesthetic; four stated that they were not. Intravenous morphine before reduction was recommended in several conferences. One officer reported the use of a local anesthetic; he injected one ounce of 1 per cent procaine directly into the shoulder joint before reduction.

The question of the optimum maneuver for the reduction was frequently discussed. Only two officers stated that they were using the Kocher technique. Of the other methods, three were described as follows:

1. The "three sheet method," in which one sheet is applied around the chest high in the axilla for a pull across the chest, a second sheet around the forearm with the elbow flexed for a pull down on the arm, and a third sheet high on the upper arm for a pull outward from the chest wall.

2. Pulling the extremity straight out in abduction, with countertraction provided by the operator's foot against the chest wall or by an assistant who pulls on a folded sheet placed in the axilla and across the chest wall.

3. Pulling downward on the arm while an assistant pushes the head of the humerus upward into the glenoid cavity.

For primary dislocations, the time of immobilization, as well as the type of immobilization, was frequently discussed. A Velpeau dressing for ten days, followed by a sling for two to three weeks, was advised by some officers. Others advocated four to six weeks of immobilization. One consultant was of the opinion that six weeks was much too long for this immobilization. For a period of eight weeks after removal of the initial dressing, one officer was using a leather buckle brace around the upper arm and chest wall to prevent abduction of the shoulder.

Another officer aptly emphasized the necessity for asking the physical training instructors not to attempt to reduce shoulder dislocations when they occur during physical training.

One physician described a "rotary dislocation" in which the head of the humerus appeared to have turned completely around in the glenoid without coming out. He stated that this type of dislocation may be very difficult to visualize roentgenographically.

An officer from a general hospital reported five unreduced shoulder dislocations which appeared many weeks after the original injuries.

*b. Recurrent.*—The frequency with which recurrent dislocations of the shoulder are being observed in the Army is certainly an indication

that something is wrong with what is considered orthodox treatment of the original dislocation.

The Nicola procedure is the most popular operation for recurrent dislocation at this time, although the Bankart operation has many ardent supporters. The largest number of operations reported from one hospital was forty Nicola operations over a period of sixteen months.

Many poor results following Nicola operations are now appearing in the hospitals and dispensaries. In one general hospital, it was reported that eighteen patients who had had the Nicola operation were complaining of painful scars, and that nine of these patients had had a recurrence of the dislocation after operation. In a second general hospital, three postoperative dislocations had been observed. In a third general hospital, five Nicola operations had been performed and two recurrent dislocations following Nicola operations done elsewhere had been observed. It was stated that a follow-up of forty-seven Nicola operations performed at the University of Michigan had shown a recurrence rate of 15 per cent. It is believed by many that a similar or higher percentage obtains in the Army. This is to be compared with a recurrence rate of 4.6 per cent recently reported by Dr. Nicola.

An officer who had been associated with Dr. Nicola in civil practice was of the opinion that the principal reason for the large number of poor results is faulty operative technique. In a very careful review of the technique of operation and postoperative care as now advocated by Nicola, he emphasized the following:

1. A capsular strip one-half inch wide, left attached superiorly, should be pulled through the tunnel in the humeral head along with the biceps tendon. This provides strong reinforcement of the tendon.

2. The tunnel should be placed at an angle of 45 degrees to the shaft of the humerus. Failure to place the tunnel properly, he considered the most common cause of recurrence.

3. Care should be exercised not to injure the branch of the circumflex nerve which supplies the anterior portion of the deltoid muscle.

4. The shoulder should be immobilized for seven to ten days following operation. Abduction exercises should then be started, but the elbow is not to be extended beyond 90 degrees for three weeks; full use of the arm is not allowed until three months after operation.

One officer did not like the Nicola technique and used a modification of Roberts' technique, that is, placing the biceps tendon in a trough lateral to the bicipital groove. The trough is formed by lifting up a flap of bone and, after the tendon has been put in the trough, the flap is replaced. Postoperatively, a shoulder spica cast was worn for four weeks and full duty was not allowed for three months. The Bankart operation was



favorably reported on in two conferences; it is believed by many to result in a more stable shoulder and fewer recurrences than does the Nicola operation. One officer described the Cayo operation for recurrent dislocation; in this procedure the origin of the teres major muscle is transplanted from the scapula to the top of the shoulder.

It was repeatedly emphasized that a shoulder which has been dislocated postoperatively cannot be expected to stand up under the stress and strain of the obstacle course for commando training. Nevertheless, many soldiers with such shoulders are required to participate in these activities.

One officer stated that he had never seen a dislocation in a shoulder with a previous paralysis of the deltoid muscle.

(*Comment.*—The evidence on dislocations of the shoulder indicates that more attention should be given to immobilization of the original dislocation. If this is done, there will in all probability be fewer recurrent cases. I believe that the period of immobilization should never be less than three weeks and that preferably it should be six weeks. The routine use of a shoulder brace to prevent abduction for an additional period of eight weeks would be another safeguard against recurrence.

More careful selection of recurrent cases for operation should be made and the operation should be done only by those who are trained and experienced in its technique. The faulty technique of the inexperienced surgeon is undoubtedly one of the principal reasons for the high incidence of recurrences in the Army. I believe that the soldier who has had an operation for recurrent dislocation should never be qualified for full military duty.

The advocates of the Bankart operation believe that it results in a far more stable shoulder, less likely to be dislocated than following the Nicola operation. I have had no personal experience with the Bankart operation and cannot express an opinion concerning it; I believe, however, that it is worthy of consideration by more surgeons.)'

### 5. *Miscellaneous Shoulder Conditions*

A case of a loose body within the shoulder joint was reported; the loose body caused a slipping sensation which a patient might confuse with dislocation.

It was recommended by one physician that every injured shoulder be examined carefully for damage of the axillary nerve, and that nerve suture be done immediately if evidence of rupture should be found.

(*Comment.*—It is doubtful whether rupture of a nerve can be ascertained immediately after injury. It would be better to delay operation until there is definitely no evidence of return of nerve function.)

One officer recommended strongly that lateral x-ray pictures of the shoulder, as well as the standard anteroposterior x-rays, be made routinely. The anteroposterior ones should always be taken first with the

arm in internal rotation and then with it in external rotation. Often one view will show an abnormality which does not appear in the other.

(*Comment.*—The lateral x-ray picture of the shoulder should be made with the x-ray tube in the axilla and the film on top of the shoulder while the arm is held in abduction.)

The treatment of painful subdeltoid bursitis, with and without calcareous deposits, was discussed in several conferences. There were numerous reports of relief of pain by needling, procaine injection, or irrigation of the bursa.

(*Comment.*—These procedures are certainly generally accepted for acute subdeltoid bursitis. Satisfactory results are being reported from all clinics.)

### 6. *Fractures of the Head and Neck of the Humerus*

Two officers were of the opinion that a fracture of the greater tuberosity with displacement always required an open operation whereby the tuberosity is fixed to the head with a peg or nail. Two physicians stated that for a fracture of the greater tuberosity the arm should be held in a position of adduction rather than abduction, as the latter position has a tendency to displace the fracture fragment. This is contrary to the usual teaching.

The hanging-cast method of treating fractures of the neck of the humerus was discussed at several conferences. Two officers were strongly in favor of its use for these fractures and one was just as strongly opposed. One physician reported eight good clinical results in a series of ten cases of fractures of the surgical neck of the humerus treated by the hanging-cast method.

(*Comment.*—The hanging-cast method is as valuable for the treatment of the uncomplicated fracture of the neck of the humerus as for the shaft and should be employed wherever possible.)

## PART II. FRACTURES AND DISLOCATIONS OF THE ARM, FOREARM, AND ELBOW

The group of fractures and dislocations of the arm, forearm, and elbow does not constitute so high a percentage of the total fractures and dislocations in the Army as in civil practice. This group comprised twenty-eight cases or 5 per cent of the 580 fractures reported by one hospital. Of the arm, forearm, and elbow injuries, fractures of the head of the radius form the most common as well as the most serious problem.

### 1. *The Shaft of the Humerus*

According to the statistics, fractures of the shaft of the humerus in the Army Air Forces hospitals are relatively common. The main discussion in every conference concerned the value of the hanging-cast method of treatment. Three series of fractures of the shaft of humerus, of twenty, seven, and five cases respectively, were reported; in each

series the hanging cast had been employed with strong union of all fractures in a normal length of time. There was only one physician who did not prefer this method to all others for the treatment of these fractures. He was using skeletal traction through the olecranon with the arm in a shoulder spica at 90 degrees abduction. It was repeatedly emphasized that with the hanging-cast method great care should be taken to prevent distraction of the fragments. Frequent x-rays are indicated in the early stages of the treatment. In one hospital a very light arm cast was used and a small shot bag was fixed under the elbow portion of the cast. The weight of the cast could be varied by increasing or decreasing the shot in this bag.

It was the opinion of many of the officers that the hanging cast could be applied satisfactorily in the casualty station of the combat area. They recommended that under such circumstances the arm be fixed to the trunk for comfort during transportation. This additional immobilization can be secured by applying a plaster splint over the cast across the shoulder to the neck and firmly securing cast and splint to the chest wall with bandages.

One physician was of the opinion that if reduction of a fractured humerus could not be obtained by a few days of conservative treatment, operation should be carried out and the fragments plated.

(*Comment.*—The value of the hanging-cast treatment of fractures of the shaft of the humerus has now been clearly demonstrated over a period of eleven years. The method has come to stay; the few bad results are most often due to failure of the surgeon to apply properly the accepted technique. For ten days to two weeks following fracture, the patient should not be allowed to assume a position in which the weight of the cast is not pulling down on the lower fragment. This will present little difficulty if the principle of the hanging cast is explained to the patient and his cooperation is secured. The surgeon should never allow distraction to occur, but should check with frequent x-rays in the first few days following application of the cast. If distraction is present, either the weight of the cast should be decreased or a new and lighter cast should be applied after gentle manipulation of the fragments into better position. Circumduction and rotation exercises of the shoulder should be started early and continued until the patient returns to full duty.)

## 2. *Fractures Involving the Condyles and Lower End of the Humerus*

There were frequent discussions of the operative versus the non-operative treatment of extensively comminuted fractures of the elbow. Dr. John Dunlop of Pasadena, Calif., reported several most satisfactory long-term end results in patients treated by the skin traction method which he first described in 1927 and which he still believes to be the best method for treating extensively comminuted fractures of the lower end of the humerus. This method was advocated also by two officers at

other conferences. Dr. Dunlop stated specifically, however, that if fractures of the condyles could not be brought into good alignment with the closed method, open operation should be performed and internal fixation used as indicated. Several officers expressed the opinion that open operation was indicated only if the closed method did not give a good anatomic result. Two physicians recommended the use of small Kirschner wires for the fixation of displaced condyles. One officer was using small plates and screws to fix the fragments of the T fracture. Two officers recommended the use of skeletal traction, with a Kirschner wire through the olecranon, for all fractures about the elbow which require traction. Many advised that this traction be applied with the shoulder in a spica cast in 90 degrees abduction. An officer and a visiting physician strongly recommended this type of immobilization for supracondylar fractures when traction is not required to maintain the reduction; they advised the spica cast particularly for children, because of the considerable danger that the fragments may slip after reduction.

(*Comment.*—Conservatism in the treatment of the extensively comminuted and displaced fracture of the elbow undoubtedly gives the greatest number of good results in the hands of the largest number of surgeons and should therefore be advocated for military surgery. The displaced single condyle which cannot be held in proper alignment should be fixed with a screw, wire, or nail, but I believe that there are very few other fractures of the elbow, with the exception of olecranon fractures, which should require open reduction.)

### 3. *The Head of the Radius*

In all conferences there was considerable discussion of the treatment of injury of the radial head. For incomplete fractures of the head of the radius or complete fractures without displacement the trend is distinctly toward early mobilization. When immobilization was used, it was seldom continued for more than two weeks. One officer recommended the application of hot packs every two hours for two days, followed by active motion and triceps exercises. In all conferences emphasis was placed upon active rather than passive motion. Two officers stated that if hemorrhage is present it should be removed from the fracture site by aspiration before motion is instituted.

For comminuted and displaced fractures of the head of the radius, early excision of the fragments and the head was recommended. Many officers believed that removal of the displaced fragment or fragments was sufficient if the fracture involved less than one-third of the articular surface. There was considerable variance in opinion regarding the choice of skin incision for approach to the head of the radius. One officer recommended a posterior incision, a second officer a posterolateral incision, and a third and a fourth officer an anterior incision. The

latter two believed that an anterior approach entailed less danger of subsequent extra-articular calcification.

There were numerous reports of excessive calcification about the elbow joint following removal of the head of the radius. One officer reported two patients observed in civil practice in which this abnormal calcification had caused complete ankylosis of the elbow, while a second officer reported two similar cases with only 5 and 10 degrees, respectively, of elbow mobility remaining. A third officer stated that this extra-articular calcification could be minimized by two weeks of immobilization following the removal of the head. Two officers believed that a good method of minimizing excessive extra-articular calcification after operation is to cover the end of the radius with muscle and soft tissue after excision of the fracture fragments and the remaining portion of the head. Everyone agreed that, if indicated, excision of the fragments and remaining portion of the radial head should be performed early, preferably on the day after fracture; however, it was very wisely stated "if there is any doubt as to whether the radial head should be removed, operation should be deferred until it is definitely established that removal is necessary for good function." It was stated at several conferences that, if not performed early, the operation should be delayed for several weeks.

It was stated that two other disabling complications following the removal of the head of the radius are: (1) radial deviation of the wrist with subsequent pain and weakness and (2) lateral instability of the elbow.

Thirty patients with fracture of the head of the radius were treated at one hospital as follows: twenty-four by the closed method with an average hospital stay of thirty-one days, and six by open operation with an average hospital stay of fifty-two days. Those patients upon whom motion was started not later than the fifth day definitely had the better end results in both groups.

A second hospital reported twelve cases in a period of fifteen months, five patients treated by the open method and seven by the closed. A third hospital reported six patients who were treated by the closed method and three by open operation, with excellent end results in eight of the nine. In the ninth case the patient required operation and slight limitation of flexion resulted.

(*Comment.*—The reports of excessive calcification following removal of the fractured head of the radius with resultant loss of elbow motion emphasize the extreme care which must be exercised in removing every small fragment of bone and periosteum. Whether the more difficult anterior approach will minimize this undesirable calcification, I cannot say, but this incision is definitely worth considering. When operation is indicated it should always be done either very early or very late, that is, after several weeks, and never during the period of new bone production immediately following fracture.

I have never observed lateral instability of the elbow or radial deviation of the wrist following removal of the radial head; I do not believe that they would constitute serious complications in adult patients.)

#### 4. *Olecranon*

At several conferences the advisability of removing small comminuted fragments in olecranon fractures was discussed. One officer had removed the smaller fragments, carefully reapproximating the tendinous structures of the triceps tendon and maintaining approximation of the main fragments to the shaft with a screw. A second and a third officer had removed all of the proximal fragments.

(*Comment.*—I believe that it is a dangerous procedure to remove too many fragments of the olecranon following a comminuted fracture. I am definitely opposed to the complete excision of the olecranon process which is being advocated by some surgeons at this time.)

#### 5. *Monteggia's Fracture*

The treatment of the syndrome of fracture of the upper third of the ulnar shaft and anterior dislocation of the head of the radius was frequently discussed, but only a few cases were reported. One physician suggested treating the ulnar fracture by inserting a Steinmann pin through the olecranon into the ulnar shaft and across the fracture line into the lower fragment. He was of the opinion that reduction of the dislocation of the radial head could be maintained by flexing the elbow after the ulnar fracture had been fixed in this manner. Excision of the head of the radius and this use of a Steinmann pin were suggested by another physician. An officer reported satisfactory results from plating the fractured ulna and constructing a fascial sling to hold the head of the radius in place, while two physicians recommended plating the ulna and repairing the orbicular ligament of the neck of the radius. There were no reports of the end results of any of these methods of treatment.

(*Comment.*—Constructing a fascial sling or repairing the orbicular ligament to hold the dislocated head of the radius in place is a difficult operative procedure and should only be attempted by those who have been trained in this type of surgery. Excision of the dislocated radial head is indicated if its reduction cannot be maintained but should not be done as an initial procedure.

Open operation with plating of the ulnar fracture is always to be preferred to external fixation of the fracture with a Steinmann pin.)

#### 6. *Dislocation of the Elbow*

Dislocation of the elbow was frequently the subject of discussion. One officer advocated using an elbow sling for a period of two to three weeks after reduction and then allowing motion. A second officer re-

ported two previously unrecognized posterior dislocations of the elbow amongst overseas casualties. A third officer reported the very unusual combination of a posterior dislocation of the elbow with an olecranon fracture. This was followed by an excessive amount of extra-articular bone formation; however, with splinting and rest this abnormal bone completely disappeared.

(*Comment.*—I have personally seen large masses of abnormal calcification in muscles and in and about joints completely disappear with immobilization in plaster for periods of from eight to twelve weeks. I strongly recommend this treatment for all complications of this type.)

### 7. *Aftercare of Elbow Fractures and Dislocations*

The point was stressed in four conferences that under no circumstances should the manipulation of a stiff elbow after fracture or dislocation be allowed. Several tragic examples of such manipulation were reported. It was further emphasized by one officer that passive stretching, carrying weights, and hanging by the arm from a bar are all contraindicated. It was stated that too often the additional injury of the elbow by manipulation, forced passive motion, and stretching will result in a permanent decrease of mobility rather than an increase. Many officers were of the opinion that the recovery of mobility of the elbow following injury should be accomplished only by active use of the joint.

(*Comment.*—Too much stress cannot be placed upon the disastrous results which may follow manipulating and passively stretching an elbow after injury. The occasional good result does not justify the use of these procedures.)

### 8. *Volkmann's Contracture*

This condition must fortunately be extremely rare amongst military personnel, as no cases were reported at the twelve conferences. I have personally observed but one case in the Army. One physician, however, reported five civilians with circulatory embarrassment of the forearm and hand following elbow fractures; these were treated by procaine injection of the stellate ganglion and brachial plexus with improvement of the circulation. It was the opinion of this physician that each case represented a potential Volkmann's contracture.

(*Comment.*—Procaine injections of the sympathetic ganglia are being performed to improve the circulation in more and more conditions involving the extremities. Many times I have seen embarrassed circulation improve with such injections and I am of the opinion that this method should now be employed as a routine procedure in these conditions.)

### 9. *The Shafts of the Radius and Ulna*

There was little discussion of fractures of the forearm. Two officers recommended open operation on all displaced fractures, a plate being

used on one or both of the fractured bones. Two other officers stated that, if open operation is indicated, two incisions should be used rather than one because they entail less likelihood of synostosis from excessive calcification.

### PART III. FRACTURES AND DISLOCATIONS OF THE HAND AND WRIST

Fractures and dislocations of the hand and wrist comprise the largest group of injuries observed in the Army Air Forces hospitals and dispensaries, constituting from one-third to one-half of the total number of fractures and dislocations. The common conditions divide themselves into four groups: those of the lower end of the radius, the scaphoid, the metacarpals, and the phalanges.

#### 1. *The Lower End of the Radius*

*a. Incidence.*—Fractures of the lower end of the radius are not so commonly observed as in civil practice. A considerable number of Colles fractures, are reported; many of these, however, are actually other fractures of the lower end of the radius rather than the true Colles type. One hospital reported three fractures of the lower end of the radius in a series of 100 fractures of the hand and wrist; a second hospital reported 15 in a series of 280 fractures of the hand and wrist; this is an incidence of 4.7 per cent for the two hospitals. This figure is to be contrasted with an incidence of 11 per cent which was reported from the Massachusetts General Hospital Fracture Service several years ago. A third hospital reported 4 fractures of the lower end of the radius in a series of 110 fractures of the wrist alone. On the basis that fractures of the wrist make up approximately one-fourth of the group of fractures of both the hand and wrist, the incidence for the third hospital would be only .9 per cent.

(*Comment.*—A probable explanation is that the third hospital serves a field which is a cadet center, where the average age is approximately 20 years as compared with an average age of approximately 27 years on the other two fields. All fracture statistics show that fractures of the lower end of the radius are more common in the older age groups than the younger. This also explains the different incidence in the statistics from the Massachusetts General Hospital, where the average age of fracture patients is considerably higher than in the Army.)

*b. Reduction and Immobilization.*—The complete or nearly complete Cotton-Loder position of flexion and ulnar deviation after reduction was used for plaster immobilization by four officers. One of these officers was including the thumb to provide more rigid fixation of the hand. Two officers condemned the use of the full Cotton-Loder position because of the dangers of median nerve injury and of stiffness, and in its place recommended a position of slight flexion and ulnar



deviation. Two other officers recommended a neutral position. Only twice was it stated that the elbow was immobilized in treating these fractures.

(*Comment.*—This is surprising, as many doctors in civilian practice routinely incorporate the elbow in plaster after reduction of a Colles fracture.)

The officers who employed the full Cotton-Loder position spoke of changing the position to one of decreased volar flexion after two to three weeks; however, one officer was maintaining this position for six weeks. Two officers reported the use of wire traction through the base of the first metacarpal or the bases of all the metacarpals in order to maintain reduction in extensively comminuted fractures of the lower end of the radius.

Two officers enthusiastically recommended the traction method of Joldersma for reduction of fractures of the wrist. This is the use of fifteen pounds of traction on the hand, obtained through special finger splints, for a period of fifteen minutes.

*c. Anesthesia.*—Six hospitals reported the use of local anesthesia for the closed reduction. However, general anesthesia was more often used than local. Brachial block was occasionally the anesthesia of choice.

The only poor results were reported from hospitals where local anesthesia had been used. In one report there were three malunited Colles fractures in a series of fifteen cases.

One officer was strongly of the opinion that in the reduction of a Colles fracture "the operator should not be timid, but be brutal." He believed that the unsuccessful reduction of many of these fractures was due to the fact that the surgeon did not use sufficient force. This officer strongly condemned the use of local anesthesia, believing that with its employment there was too frequently an inclination on the part of the surgeon to stop short of a complete reduction because of the pain suffered by the patient due to incomplete analgesia.

(*Comment.*—It is my opinion, substantiated by this evidence, that local anesthesia should not be the anesthesia of choice in the Army for reduction of the fractured wrist, except in unusual circumstances.)

## 2. Scaphoid

*a. Incidence.*—The frequency of fractures of the scaphoid bone as contrasted with other fractures of the wrist is most striking. One hospital reported 91 fractures of the scaphoid in 110 fractures of the wrist alone, or an incidence of 80 per cent of the fractures of the wrist. A second hospital reported 47 in 280 fractures of the hand and wrist, while a third hospital reported 12 in 100 fractures of the hand and wrist; this is an incidence of 15.5 per cent of the hand and wrist fractures in these two hospitals. In one hospital with complete fracture

statistics for one year, the incidence was 8.1 per cent, which is to be contrasted with the incidence of .5 per cent in civilian life, stated by Key and Conwell in their textbook on *Fractures and Dislocations*. Six hospitals reported having treated the following numbers of scaphoid fractures: 91, 47, 23, 16, 12, and 9, or a total of 198.

*b. Diagnosis.*—In all the conference reports on these fractures there was little mention of the “sprained wrist” which later showed a scaphoid fracture, a condition so frequent in civil practice.

(*Comment.*—This is probably due to: (1) a more frequent use of the x-ray in the Army than in civil practice and (2) the medical officer’s constant vigilance in looking for a scaphoid fracture in the injured wrist.)

One officer reported that tapping on the end of the finger tips will cause pain in the wrist in a large percentage of the cases of fractured scaphoid. A second officer stated that pressure against, and traction on, the thumb will often produce pain about the scaphoid if it has been fractured. A third officer reported a “ring sign” in the x-ray of the wrist as follows: “Fractures of the central portion of the bone are usually on somewhat of a tangent. Due to the fact that the breaks in the dorsal and volar cortices are not superimposed, these breaks will be seen as two lines, which fuse at the lateral aspects of the bone to form a ring.”

In one series forty-five of forty-seven fractures occurred across the body or waist of the bone. Repeated emphasis was placed upon the fact that fractures of the waist were more serious than fractures of any other portion. Apparently, a bipartite scaphoid, which may be confused with a fracture, is more frequently observed than is generally believed. At one conference there were seven officers who had observed a bipartite scaphoid in the Army.

*c. Immobilization.*—It was agreed in every discussion that firm plaster fixation of the wrist, extending from the elbow to the knuckles posteriorly and the crease of the palm anteriorly and including the thumb, was essential for solid union. Ten hospitals reported immobilization of the thumb in abduction with the wrist in radial deviation. Five of the ten insisted that the plaster be extended to the tip of the thumb, while the other five carried it to a point just proximal to the phalangeal joint of the thumb. One officer believed that it was unnecessary to abduct the thumb but that it should be held firmly in plaster in a neutral position; however, he insisted that the plaster be well molded into the palm in order that the cast obtain a firm grip on the hand.

It was agreed at all conferences that immobilization should be continued until the fracture showed x-ray evidence of healing; this period usually is about twelve weeks. Many stated that union would occur in sixteen to twenty weeks; however, one officer expressed the opinion that it might occur in six weeks.

*d. End Results.*—The combined reports on the end results from six hospitals showed 195 of 198 scaphoid fractures, or 98.5 per cent, healed with solid union. This is to be contrasted with the average of approximately 80 per cent which is stated in some textbooks.

(*Comment.*—The explanation of this high percentage of unions is undoubtedly (1) early recognition and (2) proper treatment. It must be remembered that these figures are from hospitals with well-qualified orthopedic surgeons. The percentage of unions for all Army Air Forces hospitals and dispensaries would not be this high but would probably be well above 80 per cent.)

*e. Nonunion.*—Two officers preferred bone grafting for the old ununited fracture, but they reported only one good result. A third officer reported three patients who had bone graft operations performed with poor results and who were later discharged from the service on account of painful wrists. Each of two other officers reported one good result from drilling across the fracture line in an old nonunion. Another officer advised removal of the proximal fragment; however, four poor results following this procedure were reported.

It was generally agreed at all conferences that the results of operations for nonunion seldom allowed return to full military duty. Two officers stated that for military service the wrist with a nonunion of the scaphoid was generally preferable to the postoperative wrist, even though union had been obtained.

At one conference there were reported several patients whose x-ray pictures showed evidence of old fracture but who denied having had any wrist pain previous to the occurrence of a recent accident. The explanation is probably that these patients had old fractures with previous asymptomatic nonunions.

(*Comment.*—These reports on scaphoid fractures show that:

1. There is a high incidence of these fractures, especially among the younger soldiers at the cadet centers.
2. With early recognition and adequate treatment, a high percentage of unions can be expected.
3. In the Army, operative treatment of the old ununited fracture seldom leads to a good result and hence is never indicated, except for the soldier who can be placed on limited duty.
4. A bipartite scaphoid should always be looked for and, if suspected, should be investigated further by x-ray examination of the other wrist.
5. Many old ununited fractures are asymptomatic.)

### 3. The Metacarpals

*a. Incidence.*—One hospital reported thirty-two fractures of the metacarpals in a series of 280 fractures of the hand and wrist, an incidence of 12 per cent; another hospital reviewed a series of twenty-four fractures.

*b. Treatment.*—At all conferences it was agreed that a displaced fracture should be treated with skeletal traction, especially a fracture of the Bennett type (fracture dislocation of the base of the first metacarpal). One officer reported twenty-six good results in thirty-two metacarpal fractures following the use of skeletal traction through the nearest phalanx. A second officer expressed a dislike for skeletal traction; he recommended skin traction obtained by using stockinet with a cellulose acetate preparation applied on the fingers and/or thumb. In another hospital, traction was obtained by the application of a towel clip through the distal end of the metacarpal just back of the head. This method is particularly applicable to fractures of the first metacarpal, especially the Bennett fracture, but can also be used for fractures of the second and fifth metacarpals.

Two officers disapproved of the use of a "roll of bandage" in the palm for immobilization of a metacarpal fracture, objecting to the resultant stiffness. One consultant was of the opinion that the best treatment for fractures of the metacarpals and phalanges is two weeks of immobilization, followed by a period of active physical therapy. He believed that too frequently the prolonged immobilization of these fractures is followed by poor results.

Knuckle fractures or fractures of the metacarpal neck were discussed in all conferences. The reduction was being satisfactorily accomplished in two clinics by flexing the metacarpophalangeal joint and pushing upward (in a dorsal direction) on the first phalanx and downward (in a volar direction) on the shaft of the metacarpal. Immobilization in this position was being secured by the use of plaster.

In undisplaced fractures of both the metacarpal bone and phalanx, one officer described excellent results following the injection of procaine into the fracture site and the early institution of motion.

Five officers discussed the use of Kirschner wires through two or more metacarpal shafts for immobilization of the fractured metacarpal, after the method described by Waugh, and Berkman and Miles. From one to three wires were inserted, and motion of the fingers and hand was started immediately. One officer reported a soldier who returned the next day to work as a mechanic. However, there was a report of two cases of infection of the hand following the use of this method.

One officer reported an arthrodesis of the first carpometacarpal joint because of pain in the hand following a Bennett fracture. Following this operation the hand showed excellent and painless function.

(*Comment.*—The Kirschner wire method for immobilization of fractured metacarpals should definitely be used only in selected cases, as the reports of infection of the hand show that the method is attended by an element of danger which cannot be disregarded.)

#### 4. *Phalanges*

*a. Incidence.*—Fractures of the phalanges are by far the most common of all. One hospital reported 177 in a total of 280 fractures of

the wrist and hand, an incidence of 63 per cent. Another hospital reported that fractures of the proximal phalanx constituted 50 per cent of all fractures of the hand.

*b. Baseball or Mallet Finger.*—Baseball or mallet finger was discussed at all conferences. The results were in general so unsatisfactory that in many hospitals open operation had been frequently used in an effort to find a more satisfactory solution. However, one of these hospitals reported eight poor results out of ten patients operated upon, the operation having been followed by suppuration and the extrusion of black silk sutures. Needless to say, this hospital had discontinued the procedure. Two officers reported an open operation with the use of wire, tantalum in one instance and steel in the other. The ends of the wire suture were allowed to protrude through the skin, and later the suture was removed. Two good results, after six and twelve months, respectively, were reported with this procedure. The same procedure with the use of silk instead of wire was reported by another officer; his results were not given.

Everyone agreed that the correct position for the splinting of the finger is one of hyperextension of the distal phalangeal joint accompanied usually by flexion of the proximal phalangeal joint. This position was being maintained in two clinics by the use of a plaster thimble which extended from the tip of the finger to a point proximal to the first interphalangeal joint. The immobilization time was usually three to six weeks. One officer reported maintaining this same position by means of a circular adhesive dressing, beneath which felt pads were placed at the tip of the finger and distal end of the proximal phalanx. One hospital reported unsatisfactory results in 50 per cent of all patients who were treated with splints.

One officer stated that flying personnel with baseball fingers frequently reported the fact that at approximately 15,000 feet they were unable to use these injured fingers.

*c. Treatment of Fractures of the Phalanges.*—Skeletal traction was being rather generally used to maintain position of the fragments, especially when the fracture was near a joint and the fragments displaced. One officer reported inserting a surgical needle under the attachment of the flexor tendon to the terminal phalanx for traction. A second officer cautioned against the use of a motor saw in inserting wires through phalanges for skeletal traction.

A hairpin splint was being used in two clinics for the immobilization of the distal phalanx. A third officer reported the satisfactory use of the one 1/4 inch steel tape from packing cases as a splint material.

A fourth officer reported improvement in finger function from arthrodesis of an interphalangeal joint after severe intra-articular fractures of the phalanges. The position of ankylosis was one of slight flexion.

(*Comment.*—The evidence certainly does not favor open operation for the baseball finger.

Arthrodesis for the malunited intra-articular fracture should be performed as a last resort and only when it is necessary for the relief of pain.)

#### PART IV. FRACTURES AND DISLOCATIONS OF THE HIP, THIGH, AND KNEE

The problems involved in injuries of the hip, thigh, and knee are fortunately seldom observed in the Army Air Forces station hospitals. Because these hospitals usually evacuate patients with major fractures, including most of this group, to the general hospitals, the reports from these station hospitals are not of great significance. At the conferences, reports were given of six patients who had fractures of the femur and who died of fat embolism following transportation to another hospital; all of these patients had been transported soon after injury. This information should sound a note of warning concerning too early transfer of patients with major fractures to other hospitals.

##### 1. *Fractures of the Hip*

Fractures of the hip definitely do not constitute a problem in the Army hospitals. It is rather interesting to note that in a report of 366 cases of fracture of the hip in civil practice, there were only thirty-four patients, or 9 per cent, between the ages of 18 and 45 years, which are the age limits for induction into the Army.

There was a report of fifty patients treated in civil practice by the use of four Moore nails, with a follow-up of one year or longer. Solid union was present in 90 per cent of the hips. This percentage, of course, is much higher than that reported by most advocates of nailing for fractures of the hip.

At one large general hospital only two hip fractures were observed over a period of three years. One of these was malunited and the other ununited.

One officer reported the following operative procedure for nonunion of fracture of the hip: a subtrochanteric osteotomy was performed; a blade type of nail plate, such as is made for intertrochanteric fractures, was then used in a reversed position to hold the fragments approximated in their new alignment.

##### 2. *Dislocations of the Hip*

In the Army, traumatic dislocation of the hip is observed much more frequently than fracture of the hip. In all discussions it was stated that when dislocation is associated with a posterior acetabular marginal fracture the dislocation should first be reduced; if the fragment remains displaced, an open operation is then indicated for its reduction and internal fixation.

varus or valgus, repositioning the fragments with a clamp, applying a circular cast with the knee in varus or valgus, and applying traction through the cast.

(*Comment.*—Some of the most serious fracture problems are presented by the plateau fractures which we have to treat. I believe that the depressed and displaced fracture should be exposed by open operation, the fragment or fragments restored to as normal a position as possible, and the fragments then fixed in place with a bolt, screw, or nail. Following this, early motion is indicated, but weight-bearing should be delayed for at least twelve to sixteen weeks. These fractures, despite the best of treatment, seldom result in normal, painless knees.)

#### PART V. FRACTURES AND DISLOCATIONS OF THE LEG AND ANKLE

Fractures and dislocations of the leg and ankle constitute a large problem in the Army Air Forces hospitals, since fractures and dislocations of the ankle are the most common injuries except for those of the wrist and hand.

##### 1. *Shaft of the Tibia and Fibula*

In a series of 100 fractures of the leg and ankle, there were 5 of the shaft of the tibia and 95 of the ankle, 82 of which involved only the external malleolus.

In all discussions it was generally agreed that for the oblique and displaced fracture of the tibia, in which the fragments cannot be maintained in alignment by traction, an early open reduction and internal fixation, preferably with a plate, is indicated. For fixing the fragments in long oblique fractures, one officer used two to four screws without a plate. He believed that in difficult fractures an open operation was far preferable to the risk of nonunion which might follow separation of the fragments by traction.

One officer was enthusiastic about the use of the three-section cast method in the treatment of fresh fractures of the shafts of the tibia and fibula. The upper and lower sections were first applied, then, after reduction, the middle section was added.

For treatment of the old fracture of the femoral or tibial shaft with overriding, one officer from a general hospital reported the successful use of skeletal traction obtained on a fracture table. The amount of traction was gradually increased until the overriding was corrected. The extremity was then immobilized in plaster, the pins used for skeletal traction being incorporated in the cast.

For the old fracture with absence of a section of the tibia, an officer reported the operation of fusing the lower tibiofibular joint. It was found that following this procedure the fibula often will hypertrophy to a sufficient size and strength to bear the weight of the patient.

One officer cautioned against using too much traction on the os calcis in treating fractures of the lower leg. In one patient he had observed as much as one-half inch of separation between the astragalus and the lower surface of the tibia. This stretching of the joint ligaments, he stated, might result in pain and a permanent relaxation of the ankle joint. A second officer reported that he had observed subastragalar joint pain after traction obtained by a Steinmann pin in the os calcis.

(*Comment.*—For the oblique and overriding fracture of the shaft of the tibia, internal fixation of the fragments is becoming more and more popular in many clinics and is the procedure of choice. It enables the patients to return to full military activity with fewer days lost from duty than after treatment by nonoperative methods.)

Pain and disability in the ankle and subastragalar joints after skeletal traction applied to the os calcis can probably be avoided by using no more traction than is absolutely necessary to reduce the fracture and by continuing this traction no longer than is necessary to prevent slipping of the fragments.)

## 2. *The Ankle*

How to treat fractures of the external malleolus was a subject of discussion at every meeting. It was recommended by three officers that the undisplaced fractures be not immobilized in plaster but injected with procaine, supported by strong adhesive strapping, and allowed immediately to bear weight. However, a great many advocated the use of a walking cast for a period of two to four weeks. The treatment of minor fractures of the ankle and foot with and without plaster casts was reported from an infantry camp. The average time lost from duty was without plaster, thirty-four days, with plaster, fifty-seven to fifty-eight days.

An unusual case of nonunion of a transverse fracture of the external malleolus at the level of the ankle joint was reported.

For displaced fractures of the internal malleolus, especially when the fragment is rotated, it was agreed that in most instances the malleolus should be fixed to the tibia with a nail, screw, or bone graft. It was stated that often the periosteum became interposed between the malleolus and lower tibia and prevented union. The statement was made that walking casts definitely increased the incidence of nonunion of the internal malleolus and that they are contraindicated when this malleolus is broken.

For diastasis of the tibiofibular joint, one officer recommended the use of a vitallium screw, while another officer recommended using a bolt to fix the fibula to the tibia.

For fractures of the posterior malleolus with a large displaced fragment, accurate reduction and, if necessary, fixation by a screw or nail into the tibia were recommended.



(*Comment.*—The tendency is distinctly toward open operation for more accurate reposition of fractures of the internal and posterior malleoli. The necessity for such treatment is being constantly emphasized by the large numbers of soldiers who are unable to perform full military duty because of ankle pain following these fractures.

For fractures of the external malleolus not involving the joint, early mobilization and weight-bearing should be followed by better results than is prolonged plaster immobilization without weight-bearing. If a cast is applied, it should always be of a weight-bearing or walking type.)

### 3. Sprains of the Ankle

At most conferences there was considerable discussion of the treatment of the ankle sprain without fracture. An anteroposterior x-ray picture of the ankle with the foot in inversion with or without a previous procaine injection was strongly advocated by three officers. This view often will show a separation between the astragalus and tibia which is indicative of a ligamentous rupture. If such rupture is present, suture of the torn external lateral ligaments is to be considered. One officer reported 12 cases of severe ankle sprain, in three of which the torn lateral ligaments were sutured. The results were not given. The same officer reported the repair of a torn external lateral ligament by using the tendon of the peroneus brevis muscle.

At one conference there was a demonstration of treating the severe ankle sprain by the application of a skin-tight plaster splint cast similar to the Delbet walking plaster. This extended from below the knee to the plantar surface of the heel. Early weight-bearing was encouraged. It was reported that this treatment allowed an earlier return to normal activity than did other methods.

For mild ankle sprains, procaine injection of the tender areas with immediate weight-bearing was frequently recommended. With this method some reported excellent results with little or no time lost from duty; others had tried the method and abandoned it because of unsatisfactory results.

## PART VI. FRACTURES AND DISLOCATIONS OF THE FOOT AND TOES

The incidence of injuries of the foot and toes is less than that of injuries of the ankle. Injuries to the toes are more common than are those of the foot.

### 1. The Astragalus

There were frequent references to aseptic necrosis of the astragalus following a fracture dislocation. Two physicians recommended that a subastragalar arthrodesis be performed a few weeks after this injury. Two officers were enthusiastic about the so-called wedge arthrodesis of Schrock for this fracture dislocation. In the Schrock procedure the body of the astragalus is removed; then all cartilaginous surfaces are

removed from the body as well as from the lower surface of the tibia and the upper surface of the os calcis; finally the body is reshaped to fit the space between the tibia and os calcis and is inserted therein. Two cases were reported with satisfactory end results following the Blair operation, which consists of sliding a graft down from the tibia to the head and neck of the astragalus after removing its body.

(*Comment.*—Fortunately, fractures of the astragalus are rare. It is always safe to recommend arthrodesis of the subastragalar joint when the fracture involves this joint and when there is persistent pain after healing. After fracture of the neck and dislocation of the body, there is little likelihood of a painless foot without an arthrodesis. The operations of Schrock and Blair are both sound procedures and can be recommended.)

## 2. *Scaphoid*

At one conference the unusual condition of scaphoiditis in a soldier 21 years of age was reported.

## 3. *Os Calcis*

Fractures of the os calcis are infrequently observed in the Army Air Forces hospitals. One officer recommended packing in ice the acutely swollen foot following this fracture. In all discussions emphasis was placed upon early reduction. It was reported from one general hospital that only one of approximately twenty-five compressed and comminuted fractures of the body of the os calcis among overseas casualties had been reduced before arrival at the hospital. It was reported from another general hospital among many overseas casualties only two fractures of the os calcis had been reduced.

There was frequent discussion of the best method of reduction. Three physicians were enthusiastic about the Herman method, or its modifications, for reshaping the compression fracture of the os calcis. The statement was made that in a series of over 200 cases reported by Dr. Herman from civil practice, 75 per cent of the patients had returned to work in six to nine months. One officer made the statement that any fracture of the os calcis which extended into the subastragalar joint resulted in 25 per cent permanent disability, while a second officer stated that in his experience the permanent disability had been 35 per cent.

The statement was often made that involvement of the subastragalar joint indicates a triple arthrodesis as an early operative procedure, usually within three to four weeks after the injury. In the reshaping of the compressed and comminuted os calcis, emphasis was placed on the restoration of the tuber or salient angle, formed by the plane of the subastragalar joint, projected posteriorly, and that of the posterior superior surface of the os calcis. Normally, this angle is between 30 and 35 degrees. One officer was of the opinion that gradual weight-

bearing after the healing of the fracture was preferable to immediate full weight-bearing. He recommended starting with twenty-five pounds of weight-bearing on the heel and increasing this by another twenty-five pounds each two to three weeks.

It was the opinion of one officer that a soldier with a compressed and severely comminuted fracture of the os calcis was nearly always given a certificate of disability discharge (C.D.D.).

At one conference, which approximately 150 persons attended, this question was asked: "Have you returned one or more soldiers with compressed and comminuted fractures of the os calcis to full military duty?" No officer in the audience answered this question in the affirmative. At a second conference, one officer reported two patients with compressed fractures who returned to full duty, and a second officer reported that two of three patients with this fracture returned to limited duty only. At a third conference, two nurses were reported as returning to full duty. One consultant reported that five patients with simple fractures without comminution returned to duty. One officer made the statement that the British in some instances had concluded that the end result of treatment of a comminuted fracture of the os calcis was as satisfactory without reduction as with reduction.

(*Comment.*—The evidence certainly justifies the statement that very few soldiers are returning to full military duty after sustaining a severely comminuted and compressed fracture of the os calcis.

The method selected for the reduction should always be that with which the surgeon has had most experience and has obtained best results. The Herman method or any of its modifications is excellent.

After healing, gradual weight-bearing with the arches of the foot properly supported is to be recommended.)

#### 4. Metatarsals

Metatarsal fractures are not of frequent occurrence, except those which come within the classification of "march fracture." The only discussion of metatarsal injuries other than march fractures was on the subject of avoiding plantar angulation in the treatment of fractures of the metatarsal shaft.

*a. March Fractures.*—March fractures are very common in all hospitals and dispensaries. Although some officers are still using walking casts, there has been a definite therapeutic trend toward less immobilization and earlier weight-bearing. There was one report in which thirty-seven patients with march fractures were satisfactorily treated by being retained in quarters for periods averaging ten to twenty-one days, after which strapping and an anterior arch support on weight-bearing were used.

An officer in an infantry camp reported that he had treated 105 march fractures in two years. He emphasized in diagnosis the im-

portance of dorsal pain and of always taking oblique x-ray pictures in addition to anteroposterior and lateral views. He had satisfactorily treated the last eighty fractures by splinting for the first eighteen to twenty-one days and limited walking for the next two weeks. He made the suggestion that these fractures might in some way be seasonal, as the greatest number had been observed during the month of June.

From another infantry camp came a report of 200 or more march fractures. The incidence varied from ten to forty a month and was always highest when the troops were on long marches. The treatment consisted of bed rest until the soreness disappeared and then gradual weight-bearing with an anterior arch pad in the shoe. One case of bilateral march fracture was reported.

One officer thought that stress and strain placed upon the second metatarsal head in doing "about face" or "to the rear, march" might be a causative factor.

There were reports that sixty men with march fractures had been sent to one general hospital and that forty had been sent to another general hospital. Some of these patients had been given so much prolonged rest that extensive bone atrophy, similar to Sudeck's atrophy, was present in the x-rays.

Among 313 march fractures reported from an infantry camp, 59.4 per cent involved the third metatarsal bone and 34.2 per cent the second; in the first x-ray pictures, 18 per cent showed no bone lesion and 40 per cent showed periosteal proliferation without a fracture line. This evidence substantiates the statement, made by several officers, that, "a soldier with clinical evidence of a march fracture should be treated, irrespective of a negative x-ray."

Fractures similar to a march fracture were reported as having been observed in the tibia, femur, pelvis, and ribs.

(*Comment.*—The tremendous volume of information on march fractures certainly opens up a new field of thought in bone pathology. Stresses and strains not associated with direct trauma but sufficient to cause a rupture of the normal continuity of bone have not been considered of great importance before; now that lesions similar to those in the metatarsal shafts are appearing in the tibia, femur, pelvis, and ribs, more attention must be given to the condition. The best treatment for march fractures, according to the evidence here presented, appears to consist of rest without rigid immobilization and of early weight-bearing with support of the anterior arch.)

### 5. Toes

At all conferences, emphasis was placed upon the absolute minimum of treatment for fractures of the toes, because of the danger of psychological changes in patients with overtreated minor injuries.

Officers from two Air Service Command Depots reported a very high incidence of fractures of the toes. In both of these reports, emphasis was placed upon the use of a safety shoe. This shoe has a steel covering built into the shoe over the toe which forms a definite safeguard against fracture.

It was reported from one Air Service Depot that of sixty-one fractures of the toes, fifty-four had been caused by falling objects. The treatment had consisted of only procaine injection and strapping. The average time lost from work was 2.3 hours.

One officer described a plaster moccasin for the treatment of these fractures. The use of a small Kirschner wire under the periosteum of the phalanges for fixation of the more severe fractures was reported. One physician made a plea not to soak the foot in hot water, as he believed that hot soaks made the pain worse and the disability greater.

It was stated that a foot which has had one or more toes amputated is not a good foot for military service.

(*Comment.*—Fractures of the four smaller toes should be treated as little as possible. The great toe may require more treatment than the others. Early walking after fracture of a toe is unlikely to be harmful and should be encouraged.)

#### PART VII. FRACTURES AND DISLOCATIONS OF THE SPINE AND PELVIS

Fractures of the spine are relatively common; those of the pelvis are observed much less frequently. It is reported from one general hospital that of all men with fractures admitted, 11 per cent had fractures of the spine and pelvis.

##### 1. *The Spine*

One officer made the plea that a single position be taught for transportation of men with fractures of the spine. He was of the opinion that the supine position was best and that instruction should be given regarding hyperextension of the spine for use when indicated.

(*Comment.*—The latest Army manual on first aid now teaches only the supine position for the transportation of those with a fractured spine. The British have found from experience that it is wise, in nearly all instances, to transport the patient with a fractured spine in the position in which he is found, being careful not to "fold the body.")

*a. Cervical Spine.*—The Crutchfield skull tongs are being used generally for traction on the cervical spine in fracture dislocations. One officer, however, preferred the Barton tongs. There were two reports of psychic changes following the use of tongs in the skull, that is, a "tong psychosis." At one conference a plea was made for using tongs no more frequently than absolutely necessary. One officer suggested applying fifteen to twenty pounds of traction to the tongs, taking a lateral x-ray picture of the cervical spine after fifteen to twenty minutes, and, if the dislocation is reduced, decreasing the traction to

ten to twelve pounds. He believed the tongs should be left on for a period of only three to four weeks and followed by a plaster jacket of the Calot or Minerva type.

Another officer recommended taking lateral x-ray pictures with the neck flexed if the first films were negative and fracture was suspected. It was stated that injuries of the seventh cervical vertebra were most often missed in the x-ray examination.

There was a discussion regarding fusion of the cervical spine for fracture dislocation. One officer from a general hospital reported two successful fusions for fracture dislocation. A second officer was of the opinion that in such an operation only two vertebrae should be fused. It was stated at one conference that, by means of traction, a dislocation of the cervical spine could be reduced up to six to eight weeks from the time of injury and that this was not true of dislocations in other parts of the spine.

The "two mattress" technique of allowing the head to hang over a first mattress onto a second to secure hyperextension was described. One officer preferred the Schanz cotton collar to support the head and neck in all cervical spine injuries not requiring traction or rigid fixation.

(*Comment.*—The desirability of minimizing the length of time for leaving "skull tongs" in place is evident. A "tong psychosis" may prove to be a very serious complication and the use of tongs is not always essential.

Cervical spine x-ray pictures in the anteroposterior and lateral positions should always be very carefully made. If they are negative and the clinical evidence points to bone injury, lateral x-ray pictures should be made with the cervical spine flexed as suggested.)

*b. Lumbar and Dorsal Spine.*—The question of the best type of reduction for compressed fracture of the vertebral body was repeatedly discussed. Dr. John Dunlop, of Pasadena, described his method of hyperextension with Goldthwait irons, used since 1927 on 180 cases. He reduces the compression immediately unless there is an impending paralytic ileus, in which case he waits six or seven days. He stated that paralytic ileus is a complication in approximately 30 per cent of these fractures. He was of the opinion that early ambulation is contraindicated and that bony union occurs in about four months. He, as well as another physician, made the statement that it is useless to attempt to reduce a compression fracture of the body of a dorsal vertebra above the tenth dorsal, as it is seldom possible to accomplish a reduction.

Several physicians recommended immediate reduction by forced hyperextension, application of plaster in the hyperextended position and allowing the patient to walk, in one instance in eight to ten hours after reduction and in another instance in twenty-four to forty-eight hours. In contrast with this, one orthopedic surgeon was of the opinion that these patients should be kept in bed for six to eight weeks after

injury, and another advised bed rest for three to four months. The advocates of immediate ambulation in plaster stated that it is important to maintain a snug fit by changing the cast when it becomes loosened. Several physicians stated that the cast should always be followed by a brace. It was reported that one prominent English orthopedic surgeon thought that muscle development was more important than reduction of the fracture. There was a report of pressure ischemia and slough over a part of the back after the use of a Ryerson automobile jack to secure hyperextension.

A medical officer in a processing center reported twenty-two patients with compressed fracture of the body who returned to limited duty, while one officer from a general hospital thought that most patients with fractured spines would eventually be given certificates of disability discharge (C.D.D.).

An officer from a general hospital reported several cases in which the os calcis, spine, and skull were fractured.

It was reported that a pilot who jumped from a plane felt something snap in his back as he was spinning around in his parachute. X-rays showed later that he had a compression fracture of the body of the twelfth dorsal vertebra. Eight compression fractures of bodies of the vertebrae were reported as occurring in soldiers who attempted to hold down several planes in a high wind. The mechanism of injury was the same for all, namely, forced flexion of the spine as the planes suddenly dropped to the ground after being lifted by the wind.

A case of posterior displacement of a vertebral body with complete paraplegia and herniation of the diaphragm was reported. Another report from a general hospital described six or more cases of ruptured diaphragm in overseas casualties associated with fracture of the body of a vertebra. The vertebrae involved were the sixth to the eighth dorsal.

An officer stated that arthritis often develops above and below the level of fusion for a dorsal or lumbar fracture and that fusion is seldom indicated.

*Comment*—I favor bed rest in plaster for four to six weeks after the reduction of a compression fracture of the lower dorsal or lumbar spine. This should be followed by a gradual return to walking in a plaster jacket.

The reduction of compression fractures of the middle and upper dorsal spine is never satisfactory. Some British sources have reported not attempting to reduce these fractures when there are no neurologic changes but treating them symptomatically only. The end results may be just as satisfactory with this method as with any other; however, I would favor at least six weeks of absolute bed rest as the initial treatment.

Following convalescence from a compression fracture, most soldiers should be placed on limited duty, a few may do well on full duty, but

undoubtedly many will not be able to readjust themselves to military activity and may have to be discharged from the Service.)

*c. Transverse Processes.*—It was repeatedly emphasized that when one or two transverse processes are fractured the best treatment consists of adhesive strapping and rest in bed without plaster immobilization. As in all spine fractures, physical therapy, including exercises to strengthen the back muscles, is indicated as soon as practicable. One officer was of the opinion that nearly all of these patients could be returned to duty in six weeks. To avoid the possibility of psychologic complications, a second officer emphasized the need of avoiding the term "broken back" and of telling the patient that he has a strain or sprain of the back.

*d. Spinous Processes.*—Several officers expressed the opinion that treatment of fractures of the spinous processes should be similar to that described for the transverse processes. A contrasting opinion, however, was expressed by one officer who thought that the treatment should consist of aspiration of the hematoma and immobilization in plaster in hyperextension for eight to ten weeks. If pain persisted and remained localized to the fractured area, he then advised removal of the fractured spinous process.

(*Comment.*—In the past there has been a tendency to overtreat fractures of the transverse and spinous processes. The convalescent period will be distinctly less with a minimum of immobilization and rest; the end results will be just as satisfactory. It is believed that localized pain persisting after fracture of a spinous process is due to nonunion and that the fragment should be excised.)

## 2. Pelvis

Discussion regarding fractures of the pelvis was extremely limited. Very few cases were reported. One officer from a general hospital gave the following suggestions for treatment, in addition to rest in bed on a fracture board:

1. A pelvic girdle is indicated for fractures of the anterior arch of the pelvis.
2. A suspension hammock is indicated for fractures of the posterior arch.
3. Traction should be applied to the corresponding lower extremity if one side of the pelvis is displaced upward.

One officer made the statement that weight-bearing can be allowed in four weeks if the fracture is not extensive and if the acetabulum is not broken.

A second officer described an intrapelvic approach for reduction of acetabular fractures and central dislocations of the hip.

(*Comment.*—In the treatment of fractures of the pelvis, the question of the proper time to allow weight-bearing always arises. It may be



that four weeks is a perfectly safe time in the case of simpler fractures not involving the acetabulum, but for all others, twelve weeks is the safest period.

It is my opinion that in the Army, due to the fact that trauma is often much more severe than in civil practice, more injuries of the bladder and urethra are observed in association with fracture of the pelvis.)

#### PART VIII. COMPOUND FRACTURES

The magnitude of the problem of compound fractures in time of war is exemplified in the statistics from the Veterans' Administration of World War I. From 1919 to 1926 there were 22,954 compound fracture cases in the records of the Veterans' Administration. Of this number, 4,053, or 17.6 per cent, of the men had osteomyelitis, and 4,244, or 18.5 per cent, were being compensated on the basis of a total disability. With the use of sulfonamides and penicillin in World War II, the percentage of osteomyelitis cases in the compound fracture group will certainly be less, but the totals will undoubtedly still be impressive.

As very few persons at the conferences had had actual experience in the combat areas, the discussions were, in most instances, based on experiences in station and general hospitals in the continental United States. Emphasis was repeatedly placed on the teaching that compound wounds should not be closed. However, there were reports of good results after the closure of compound wounds in station hospitals, where definitive treatment had been given within the so-called safe period of six to eight hours after injury; all of these patients were treated before the most recent directives of The Surgeon General's Office on this subject were published. Two disastrous results, however, were reported from station hospitals in cases in which the wounds had been closed and gas gangrene had developed.

(*Comment.*—In time of war there should be only one teaching on the subject of closure of the wounds of compound fractures: *They should not be closed.* There is always an element of chance in closing such a wound, and among military personnel this risk should not be taken. The report of two disastrous results following wound closure is sufficient evidence to emphasize this point.)

In nearly every clinic the treatment of compound fractures now involves the use of one or more of the sulfonamides. Sulfathiazole or sulfadiazine is often given by mouth, and usually sulfanilamide is sprinkled or dusted into the wound. One physician recommended sulfathiazole dissolved in water, however, as an instillation for wounds. One of the objections to the local use of sulfathiazole has been that it tends to cake and act as a foreign body; however, in aqueous solution it will not cake.

At this time the most pertinent subject in the discussion of infections is the place of penicillin, its use as a preventive as well as a curative agent, and its relationship to the sulfonamides. In five of the

conferences there were reports of seemingly miraculous results with the use of penicillin for infections. One physician from a general hospital reported use of the drug locally for infected areas; it was applied in the form of a wet dressing, 250 units being used per cubic centimeter of fluid.

(*Comment.*—With more information now becoming available on penicillin, which apparently is more effective than the sulfonamides, many of our ideas on chemotherapy will undoubtedly be changed. It may be that penicillin will be used eventually as a preventive agent. At the present time the volume of production of the drug is not sufficient for such use.)

A report from the North Africa theater contained the information that excellent results followed the plating of twelve compound tibial fractures through incisions away from the open wounds.

(*Comment.*—I believe that plating of a compound fracture, regardless of where the incision is made, should not be recommended for the medical officer in the combat zone. For carefully selected cases it may occasionally be an appropriate procedure.)

No large series of fresh compound fractures were reported at the conferences. The largest number of fresh cases was reported from an Army Service Force station hospital in Texas, where fifty to sixty compound fractures had been treated in ten months. The largest number of old cases was reported from a general hospital which had received 100 or more men with compound fractures from the South Pacific. They had arrived three to four months after injury. They were all in excellent condition in plaster.

One general hospital gave a report of sixty-four compound fractures among overseas casualties. Of this number, some of whom were still under treatment, it was estimated that forty-six, or 72 per cent, would be returned to military duty of some type, while eighteen, or 28 per cent, would be discharged from Service. The officer who made this report discussed gas bacillus and tetanus infections. He stated that he had never observed gas bacillus infection to begin after ten days from the time of the compound injury, nor tetanus infection after three weeks. From this observation he concluded that it would be perfectly safe to perform the secondary closure of a compound wound after a latent period of three weeks.

(*Comment.*—Three weeks is probably too early for the closure of a potentially infected wound.)

One of the outstanding reports of the conferences was made by an officer who had been with the troops on Bataan in the Philippine Campaign of 1941-1942. He reported that: (1) from 5 to 6 per cent of all hospital patients had compound fractures; (2) 90 per cent of all the wound cultures from compound fractures showed a gas bacillus; (3) all wounds were left wide open and some were irrigated with peroxide; and. (4) when indicated, early amputation was performed at the line of

demarcation of the gangrene. Final statistics showed the amazingly low mortality rate of approximately 1 per cent.

(*Comment.*—This is an outstanding result which shows what can be accomplished when certain basic surgical principles are rigidly followed.)

A group of prisoners with infected compound fractures at a Prisoner of War Camp in Texas was reported. The prisoners had recently been brought from the combat theater in North Africa. Very little sulfanilamide had been used initially on any of the wounds. Usually they had been packed only with iodoform gauze, after tincture of iodine had been applied as an antiseptic. In the series of twenty-four compound fractures, there were twelve cases of osteomyelitis.

Doctor H. Winnett Orr, of Lincoln, Neb., in discussing the treatment of compound fractures by his closed plaster method, emphasized the point that the key to the treatment is "prolonged, uninterrupted, and continuous immobilization," as originally advocated by Mr. Henry O. Thomas, of Liverpool.

The late treatment of a purulent compound fracture by débridement, plating, and dusting with sulfanilamide was reported. The result was strong union with complete healing of the wound.

A question discussed at several conferences was the correct emergency treatment of compound leg or thigh fractures in which the bone ends are dirty and sticking through the skin, particularly when such fractures occur near a well-equipped hospital. At one conference twenty-two persons were in favor of cleaning the wound and bone ends and applying a dressing and a traction splint before transporting the patient to the hospital, while eighteen were in favor of cleaning the wound and bone ends, applying a dressing and then transporting the patient to the hospital without applying a traction splint. This variance of opinion was also expressed at other conferences.

(*Comment.*—I am in favor of immediately cleaning the wound and bone ends and then applying a traction splint before transportation. This, I believe, definitely minimizes the danger of shock.)

#### PART IX. CONDITIONS INVOLVING THE BACK

The most effective treatment of the soldier with a low back complaint has been a major question on the orthopedic services of all hospitals and has in reality been the only important problem concerning the back.

##### 1. Incidence

The incidence of low back conditions in the Army Air Forces hospitals has been 15 to 35 per cent in the outpatient departments and 10 to 30 per cent, in the wards. One clinic reported that 50 per cent of those with back pain examined in the outpatient clinic were admitted to the hospital. At one processing center it was reported that in a series

of approximately 1,000 soldiers, 22 per cent of the orthopedic examinations were for low back pain.

At a large infantry training center in the South, it was reported that 320 soldiers with back pain had been admitted to the wards of the station hospital; during the same period a total of 47,900 patients were admitted to this hospital; here the incidence was .66 per cent. It was reported that a general hospital had admitted 258 soldiers with back pain during a period in which total admissions were 6,800; this is an incidence of 3.8 per cent. It was reported from another general hospital that approximately 2,500 soldiers with back pain were admitted over a two-year period; 175 were admitted in one period of two months. These figures show the magnitude of the problem.

## 2. *Symptomatology*

The complaints of the patients vary from mild backache to acute pain with or without radiation into the lower extremities.

The most significant discussion concerned the psychogenic aspect of low back pain. There is no doubt that a soldier who has a back complaint and who wants to be discharged from the Army or to be relieved from doing a disagreeable duty has a strong argument to aid in accomplishing his aim. How to differentiate the true malingerer and the mild exaggerator from the honest patient was the topic for discussion at all conferences. Some officers were of the opinion that a psychiatric examination was essential for the diagnosis and treatment of every patient with chronic back pain.

The diagnosis of rupture of an intervertebral disk was frequently discussed. A physician from a large civilian orthopedic clinic reported that 10 per cent of all the patients with low back pain and sciatica in his clinic have a ruptured disk. He further stated that it was reported from the Mayo Clinic that 13 per cent of 5,500 patients with low back pain and sciatica had shown a ruptured disk at operation. The statement was made that 75 to 80 per cent of all the patients in this group had had back pain prior to the onset of their neurological symptoms. One neurological surgeon was of the opinion that 90 per cent of all low back pain with sciatica is due to a ruptured disk. An orthopedic surgeon maintained that unless the spine were fused after rupture of a disk, there would be continued back pain due to facet changes associated with narrowing of the disk. At one conference it was stated that loss of the ankle jerk reflex is often associated with sciatic neuritis in the absence of rupture of a disk.

Back and leg pain may come from localized tender points of infection or trauma as a reflex phenomenon. It was stated that this type of pain exists far more often than it is generally believed. To differentiate this pain one officer and one visiting physician recommended the injection of procaine into the tender areas, which are termed "trigger points." If the pain is made worse when the needle is first inserted and disap-

pears with the injection of procaine, the pain is presumably referred from this "trigger point." Permanent relief was sometimes obtained by repeated injections of procaine into these points.

### 3. Classification

One officer classified these low back problems into four groups: (1) arthrogenic, (2) myogenic, (3) neurogenic, and (4) psychogenic. He reported a glove type of hypalgesia of the lower extremities in a series of 200 or more of these patients with low back pain; these cases, observed over a period of three months, he considered to be of the psychogenic type. Hypesthesia was also mentioned as being present frequently in the patients in this group.

An analysis of a series of 304 patients admitted to one station hospital was as follows: lumbosacral strain, 25 per cent; postural strain, 16.5 per cent; arthritis, 15.7 per cent; psychoneurosis, 6 per cent; spondylolisthesis, 4.4 per cent; rupture of the intervertebral disk, 1 per cent.

The following analysis of 79 patients admitted to a second station hospital over a period of one year was presented: (1) acute muscular or ligamentous strain, 29; (2) lumbosacral and sacroiliac strain, 21; (3) psychoneurosis and hysteria, 9; (4) arthritis, 7; (5) undiagnosed, 6; (6) scoliosis, 4; (7) rupture of intervertebral disk, 2; (8) spina bifida, 1.

(*Comment.*—The variance in classification of these low back conditions is striking. The adoption of a uniform classification would be of great value; however, opinions of the nature of the lesions in the different conditions vary so widely that it is doubtful whether such a classification could be adopted at this time.)

### 4. Treatment

All types of therapy were discussed and were being used. It was emphasized particularly by four officers, as well as by other physicians, that every hospital should have a definite program for the diagnosis and treatment of these back injuries and that after adoption this program should be rigidly followed. Most of the officers from station hospitals thought that because of time limitations in station hospitals, their treatment of the chronic back conditions was never satisfactory. Several were of the opinion that if no improvement was evident after two to three weeks of active treatment in a station hospital, a further disposition of the patient should be made. Many, however, did not believe that this period of time was long enough.

There were many discussions of the value of manipulation of the low back. It was the opinion of many officers that manipulations should be performed very carefully and only in selected patients.

Plaster immobilization was discussed infrequently. One naval officer reported the successful use of short plaster casts for certain types of low back pain.

It was agreed at all conferences that operative procedures for ruptured intervertebral disks should be performed only by neurological surgeons. In two conferences there was described an operative technique for placing a block of bone between the vertebral bodies after the ruptured disk tissue has been removed.

(*Comment.*—Placing a block of bone in the intervertebral space after the removal of disk tissue may result in less localized postoperative pain and weakness. It is certainly a technique which should be thoroughly tested before a final decision on its value is reached.)

### 5. *Disposition*

Of 320 patients treated at a large Army Service Forces station hospital, 248, or 77.5 per cent, were returned to duty; 44, or 13.7 per cent, were given a certificate of disability discharge (C.D.D.); and 28, or 8.7 per cent, were sent to a general hospital.

Of 304 cases reported from an Army Air Forces station hospital, 35 per cent of the patients were given a certificate of disability discharge for arthritis, scoliosis, or spondylolisthesis; 37 per cent were improved sufficiently to return to duty; 13 per cent were diagnosed as psychoneurotics and transferred to the neuropsychiatric service; 10 per cent were diagnosed as malingerers and discharged to duty; and 5 per cent had back pain secondary to a more serious condition and were transferred to other services. Another station hospital reported that 18 per cent of 79 patients were given certificates of disability discharge.

The figures on the disposition of patients in two general hospitals were most discouraging. The report from one hospital showed that of 310 patients, 72 per cent were given certificates of disability discharge and 28 per cent returned to duty over a period of one year. The report from the other general hospital showed that of 108 patients, 55 per cent were given certificates of disability discharge and 45 per cent returned to duty.

The disposition of the malingerer presents a most serious problem. If malingering can be definitely established, which is most difficult in the case of back complaint, the patient is sent back to duty or dishonorably discharged from the Army. In patients suspected of malingering, methods such as keeping the patient in bed without pajama pants and allowing him no bathroom privileges were reported from many clinics with various results.

(*Comment.*—The evidence as presented is certainly definite that the treatment of the low back complaint in the Army is unsatisfactory. It was thought by many at the beginning of World War II that having large groups of these soldier patients for observation and treatment might throw some light upon the problem. So far, the evidence does not suggest that this has occurred. It is to be hoped that, as the war goes on, the medical officers will give more careful thought and attention to this problem.)

## PART X. CONDITIONS INVOLVING THE KNEE

In the Army Air Forces hospitals, the results of care of the disabled knee are definitely better than the results of care of the disabled back. Because of the great number of soldiers now appearing in the Army Air Forces orthopedic clinics and showing poor results following knee surgery and inability to perform full military duty, the trend is distinctly away from surgery.

1. *Statistics*

It was reported from one station hospital that over a period of one year approximately 1,000 soldiers disabled by knee injuries had been observed and thirty operations had been performed, an operative incidence of 3 per cent. From a second station hospital it was reported that during the last six months approximately 3,500 hospital days were credited to knee injuries (an average census of twenty knee patients a day), and that during the last eighteen months 100 or more knee operations had been performed. From three station hospitals of comparable size, there were reports of sixty-one knee operations in ten months from one; sixty-two knee operations in thirteen months from another, and sixty-eight knee operations in fifteen months from the third.

2. *Diagnosis*

There was frequent discussion of the so-called MacMurray sign, sometimes called the "click test." This sign is a click when the knee is flexed, adducted, or abducted and the tibia externally or internally rotated on the femur. A positive click test is usually indicative of a lesion in the posterior portion of the knee, most often in the posterior horn of the semilunar cartilage. It was reported from one hospital that 20 per cent of a series of soldiers with knees operated on showed a positive MacMurray sign, suggesting an incomplete operative removal of the cartilage. It was noted by one officer that in a series of seventy-seven patients, some knees which showed a posterior tear of the semilunar cartilage at operation had had negative MacMurray signs before operation.

In one conference it was said to be important to take an anteroposterior x-ray picture of the knee with the joint flexed to 90 degrees in order to show the intercondylar fossa. This will often demonstrate a loose body or an osteochondritis dissecans which cannot be seen in the routine anteroposterior and lateral x-ray pictures. When rupture of an internal or external collateral ligament is suspected, it was recommended by one officer that anteroposterior x-ray pictures of both knees in abduction or adduction be taken in order to show the difference in the amount of separation between the tibia and femur.

Two officers reported the use of air injected into the knee joint as an aid in the diagnosis of doubtful cases. Approximately 150 c.c. of air were injected after aspiration of the joint fluid, and x-ray pictures were then made.

In routine examination of the knee after injury, one officer reported finding frequently an injury of the upper tibiofibular ligaments, which he believes is a more common finding than is generally supposed. In the seventy-seven patients with knee injuries already mentioned, "locking" was a definite sign in twenty-one acute injuries and was the predominant symptom in forty-three. In this series, localized tenderness was a persistent and constant sign.

One orthopedic surgeon was of the opinion that in acute knee injuries the most common cause of the so-called "locked" knee is flexor muscle spasm. He thought that later this may be accompanied by quadriceps paralysis or paresis.

(*Comment.*—A positive MacMurray sign is helpful in diagnosis but should by no means be considered conclusive evidence that a lesion is present in the posterior compartment of the knee. This was clearly demonstrated in the series of seventy-seven patients.

I believe that the anteroposterior x-ray picture of the knee flexed to 90 degrees should be made routinely when an x-ray picture of the knee is indicated.

Judging from my own experience and that of many others, I do not believe that air in the knee joint is of sufficient value as a diagnostic aid to warrant its use except in the occasional case.

There is no doubt that too often, when an injured knee cannot be fully extended actively or passively, the assumption is erroneously made that there is a loose body or displaced semilunar cartilage between the joint surfaces; in reality, flexor muscle spasm is often the etiological factor. In no event should surgery be considered for the acute knee injuries until sufficient time has been allowed for rest and hot applications to relax the muscle spasm.)

### 3. Treatment

*a. Conservative.*—In all conferences it was agreed that acute knee injuries should first be treated conservatively unless unusual indications for early operation were present. Most officers were treating the early case with rest in bed and hot applications with or without traction. For sprains with localized tenderness, the injection of 1 to 3 c.c. of 1 per cent procaine into the tender area and early active motion were recommended at one conference. Two doctors were of the opinion that a locked knee should never be manipulated.

It was very frequently stated that the knee with an effusion should be aspirated, particularly if the fluid is bloody, as such an effusion, if left in the joint, will predispose to the formation of adhesions. In the treatment of a series of 200 acute knee injuries in one hospital, it was reported that all except one required aspiration.

(*Comment.*—Whenever manipulation is indicated in order fully to extend a knee, it should be carried out with extreme care.



(*Comment.*—It is my opinion that only a very small percentage of patients with knee operations are discharged from the Army, although the percentage of patients who are completely asymptomatic and able to perform full military duty is low.)

### 5. *Miscellaneous Conditions*

*a. Osteochondritis Dissecans.*—Mention was made of the frequency with which osteochondritis dissecans was encountered at operation, but few statistics on the number of cases or the operative results were reported. In one series of thirty knee operations, eight disclosed evidence of osteochondritis dissecans.

*b. Pellegrini-Stieda Disease.*—There were numerous reports of Pellegrini-Stieda disease. Two officers reported that three patients treated by operative removal of the calcification had shown symptomatic improvement. Another officer stated that after operative removal the knee should be immobilized for several weeks to prevent a recurrence. Two physicians reported good results following x-ray therapy.

### 6. *Recurrent Dislocation of the Patella*

Recurrent dislocation of the patella was reported in only one conference. One medical officer reported five cases in which the patients had been operated upon with good results.

### 7. *Osgood-Schlatter Disease*

Osgood-Schlatter disease was mentioned frequently. Several officers had found that it was necessary to excise loose fragments of bone about the tibial tuberosity in order to relieve the pain in that area.

## PART XI. CONDITIONS INVOLVING THE FOOT

The problem of treatment of the painful foot in the Army is of great importance. The statement, "An Army is no better than the feet it marches on" is not so applicable to the Army Air Forces as to the infantry of the Army Ground Forces; however, all newly induced personnel in the Army Air Forces have to undergo the same rigid basic training as do infantry soldiers, and for this they require good feet.

### 1. *Incidence*

Statistics from one large infantry camp in the South show that from 0.3 to 1.0 per cent of its troop strength had foot complaints. This, of course, is not a large proportion of the troops, but it is sufficiently great to constitute a major medical problem. It is reported from two station hospitals, that 40 and 50 per cent of the orthopedic cases are foot problems.

### 2. *Foot Hygiene and Inspection*

In many conferences there was a discussion of foot hygiene. The questions of proper socks, blisters, toenails, foot powder, and inspection

of the feet after long marches were all subjects of discussion in many conferences. One officer was of the opinion that examination of the feet should always be included in the monthly physical inspection of all troops.

(*Comment.*—Too little attention is paid to the minor complaints of the foot, such as blisters, ingrowing nails, etc. A regular inspection of the feet of all soldiers after long marches should be carried out, preferably by the medical officer. This would decrease greatly the number of days that are lost from duty by soldiers who are required to be on their feet a large part of the time.)

### 3. *Fitting of Shoes*

From evidence presented at these conferences it is apparent that the proper fitting of shoes to the painful and deformed foot and even the fitting of the normal foot has not been done in a uniformly satisfactory manner. As a result, many normal feet have become painful because of the wearing of improperly fitted shoes, and many painful feet have become more painful. It was stated that after a few months of training, the length of the foot often gradually increases, and the shoe which originally may have fit satisfactorily becomes too small. It was further stated that: (1) the original shoe should be at least one-half to one size longer than the foot measurements indicate; (2) in general the shoe should be two sizes larger than that used in civilian life; and (3) care should be taken that the first metatarsophalangeal joint is at the widest part of the shoe.

Reference was made repeatedly to the Munson last for shoe fitting. This last was developed by a Colonel Munson in World War I. The Munson last includes 249 sizes, each size having a separate last. If time is taken to use the last correctly by having the soldier find the proper size for his feet, the correct fit can always be obtained. The Brannock shoe-measuring apparatus was mentioned in several of the conferences as being the type now most often used in the Army.

Several suggestions regarding the way to "break in" new shoes were made at the conferences. A method frequently used in World War I but seldom employed now is to have the recruit walk through water with his new shoes on and then march until his feet and shoes are dry. The inside of the shoe will then be definitely shaped to the form of the foot.

### 4. *Arch Supports*

At all conferences there was considerable discussion of the type and value of arch supports. In spite of such statements as, "any soldier who needs an arch support will not make a good soldier," and, "a rigid support will not be effective in the Army," most officers believed that arch supports have a place in the treatment of certain types of arch strain and relaxation. In several of the clinics, chiropodists (in one infantry camp as many as eight) are being employed to make very satis-

factory arch supports out of the leather and hard piano or saddle felt supplied by the quartermaster. At two of the conferences there was a discussion regarding the Morton type of anterior arch support. This comes forward under the first metatarsal head as well as behind the other four metatarsal heads. Morton stated many years ago that most people with complaints referable to the anterior portion of the foot have a short first metatarsal bone. One clinic had made an x-ray study of the length of the metatarsal bones in a series of patients with metatarsal symptoms and had found short first metatarsal bones in 16 per cent.

The use of cork insoles made by the Archograph machine was discussed at many conferences. At one field as many as 1,700 pairs were being supplied each month. The opinion was repeatedly expressed that these supports were not suitable for Army use because they do not stand up under the strain of long marches. Instances of partial disintegration of the support after one long march were cited.

The only reference to exercises for flat feet was made by one officer who doubted very much the value of foot exercises for the soldier.

(*Comment.*—It is very doubtful whether the soldier with the old flat foot which is beginning to be painful in military activity will become symptom-free and remain so with arch supports, exercises, and physical therapy, unless he be given work which involves a minimum of strain on his feet. This change of occupation within the Army is at times a very difficult thing to accomplish. Because it has often been impossible to make such a change, many soldiers have been separated from the service unnecessarily.)

### 5. *Rehabilitation*

One hospital reported a special rehabilitation program for soldiers with flat feet. This consisted of arch supports, special foot exercises, and gradually increasing periods of marching and drilling. The soldiers usually continued this program for three to four weeks. Many were able to return to full duty who otherwise might have been discharged from Service.

At one field a forced exercise battalion under strict medical supervision had been organized for all types of malingerers. In this group there was a high percentage of soldiers with flat feet. Many soldiers had been rehabilitated by this means.

### 6. *Surgery of the Foot*

At nearly every conference it was stated that the foot of the soldier should be subjected to as little surgery as possible. There were numerous reports of soldiers who were unable to return to full duty and whose conditions became worse after bunion operations. One officer expressed the opinion that the only operations indicated on the soldier's foot are those for hammer toes, overriding of the little toe, bunionettes, and soft corns. A second officer reported poor results from the amputation of

hammer toes and condemned this procedure. A third officer was of the opinion that in hammer toe the affected joint should be resected, while a fourth stated that hammer toes in military personnel should not be operated upon. Two officers reported successful plastic operations for overlapping fifth toes.

One officer made a plea that more attention be paid to ingrowing toenails. He reported that in his hospital one patient per thousand troops on the field per month had been operated upon for this condition with an average hospital stay of thirteen days, and that ingrowing toenails constituted from 10 to 20 per cent of all foot disorders.

(*Comment.*—After seeing so many unsatisfactory results from foot surgery in the Army, I am more convinced than ever that this type of surgery should be kept to a minimum among military personnel.

It appears that the incidence of ingrowing toenails on the field from which the report came is high. It is believed that most hospitals are not seeing so large a number as this.)

#### *7. Certificate of Disability Discharge for Flat Feet*

Apparently many certificates of disability discharges are being given because of flat feet. One camp reported 70 a week, while another reported 70 for flat feet of a total of 200. At a large Negro camp, at the time of the conference, 40 certificates of disability discharge a week were being given for flat feet. This is to be contrasted with the statement made at one conference, that from 1935 to 1940, in the regular Army, there was not given a single certificate of disability discharge for flat feet.

This discussion on certificates of disability discharge for flat feet led in each instance to consideration of malingering and exaggeration of symptoms. It was the opinion of many officers that soldiers with flat feet rapidly develop a psychoneurotic state. Statements such as the following were made:

“Flat foot is a mental disease and not a physical one.”

“No certificates of disability discharge for flat feet in our hospital, but certificates of disability discharge for flat feet and psychoneurosis.”

“Foot complainers may be psychiatric and have a conversion neurosis.”

“Flat foot soldiers should be looked after by the morale builders of the Army and not by the doctors.”

One officer was of the opinion that all foot cases should be “screened” to rule out psychoneurosis. If one were found, the soldier should be given a certificate of disability discharge. In contrast with this, a medical officer who had been in the German Army in World War I stated that no attention had been paid to the soldier who complained of flat feet.

(*Comment.*—Unfortunately, too many soldiers know that an extreme flat foot does not meet the minimum physical standards for induction into Service. If the soldier with flat foot is not happy in the work he is doing, his physical condition becomes exaggerated in his own mind and he is soon using it as an excuse for wanting to get out of the Service. When one soldier is given a certificate of disability discharge for flat feet, others will invariably appear with the same condition and ask for a discharge. Boards meeting to decide on this problem should exercise the utmost discretion.)

### 8. *Miscellaneous*

There was a discussion of what to do with plantar warts. One officer reported from 50 to 80 per cent cures with x-ray therapy. A second officer reported successful surgical treatment, two elliptical incisions being used.

Several patients with multiple painful hyperkeratoses of the feet were reported. Each of these was given a certificate of disability discharge.

Pes cavus was the subject of frequent discussion. Some officers were of the opinion that it was very difficult to treat in the Army and that the patient should be given a certificate of disability discharge, whereas others believed that with the proper arch pads, shoes, and limited exercise the feet could be made comfortable and the soldier retained in Service.

At one large basic training center, a great number of cases of tenosynovitis of the foot and lower part of the leg were reported. These patients had been successfully treated by injection with procaine and rest.

# Review of Recent Meetings

---

## REPORT OF THE 1944 MEETING OF THE SECTION ON SURGERY, GENERAL AND ABDOMINAL, OF THE AMERICAN MEDICAL ASSOCIATION

GEORGE D. LILLY, M.D., MIAMI, FLA.

THE Surgical Section of the American Medical Association convened in the ballroom of the Sherman Hotel in Chicago, Ill., on the afternoon of June 14, 1944. The chairman, Frederick A. Collier, Ann Arbor, Mich., presided, and Alton Ochsner, New Orleans, served as secretary.

George D. Lilly, Miami, Fla., presented a paper in which emphasis was placed upon the fact that even aged persons suffering from far-advanced arteriosclerotic vascular impairment of the lower extremities may be greatly benefited by interrupting the sympathetic nerve supply to the involved extremities.

Surgical removal of the lumbar sympathetic ganglia was recognized as the most desirable procedure, but Dr. Lilly advocated the use of alcoholic injection of the lumbar sympathetic ganglia in those patients whose general condition prohibited major surgery. He reported a series of his own cases in which alcoholic injection had been employed with gratifying relief of early gangrene, claudication, and night cramps. A detailed description of the injection technique was presented.

Keith S. Grimson, Durham, N. C., reported his experiences with studies regarding the effect of various sedation tests on experimental neurogenic hypertension. He concluded from his observations that such sedation tests, when employed in the preoperative study of clinical cases of essential hypertension, were of definite value in selecting suitable cases for thoraciccoabdominal paravertebral sympathectomy. He emphasized the fact that all such tests may be misleading, and that some patients who did not respond to sedation obtained a worth-while lowering of their blood pressure following a radical sympathectomy.

I. A. Bigger, Richmond, Va., reported twenty-nine cases of traumatic arterial aneurysm and arteriovenous fistulas, and called attention to the fact that the present war would produce a much greater incidence of this type of pathology. He discussed the various technical problems and presented detailed reports of his more interesting cases.

Geza De Takats of Chicago presented a study of *The Causalgic State in Peace and War*. He called attention to the importance of considering causalgia before making a diagnosis of hysteria. The neurophysiology of causalgia was reviewed in detail, and treatment was discussed. The importance of early diagnosis was stressed, and forty-five of his cases were analyzed.

Arthur W. Allen, Boston, Mass., reported that the incidence of postoperative phlebothrombosis and subsequent pulmonary embolism was extremely high in New England, especially during the winter months. During 1925, there was an incidence of 3 deaths per 1,000 operations, caused by postoperative pulmonary embolism. During 1943, this incidence was reduced by 75 per cent. The reduction

Received for publication, Aug. 28, 1944.

was brought about by early recognition of phlebothrombosis in the deep veins of the lower extremities, and prompt ligation of the deep femoral vein. Dr. Allen expressed the opinion that the vein ligation should be bilateral in most cases because the thrombosis is so frequently bilateral. He stated that the surgical staff of the Massachusetts General Hospital is now ligating some veins preoperatively as a prophylactic procedure in old, debilitated patients.

**Burrill B. Crohn** of New York presented an appraisal of the results of surgery in the treatment of regional ileitis. He analyzed the results in a series of 164 cases. Dr. Crohn's opinion, after observing the treatment of this disease for twelve years, is that simple ileotransverse colostomy cured just as many cases as the more radical procedures and involved a much lower mortality. He feels that early diagnosis and operation is most important, and that chemotherapy is of no value in this disease.

**Rawley M. Penick, Jr.** of New Orleans considered the problems involved in the treatment of congenital megacolon. He reviewed a series of thirty patients treated in New Orleans. He concluded that patients with megacolon should first be treated conservatively. Those who do not improve with medical treatment should be treated by left lumbar sympathectomy. If this does not afford relief the right lumbar sympathetics should be removed; and those who do not respond to this must be subjected to colectomy.

Thursday, June 15, officers for 1945 were elected. **Lieutenant-Colonel Daniel C. Elkins**, Atlanta, Ga., was selected as chairman, and **William Andrus**, New York, N. Y., was elected vice-president. **Alton Ochsner** was re-elected secretary.

**Carl Bearse** of Boston made a plea for early surgery in all patients with gallstones. He pointed out that early removal of the diseased gall bladder, with its stones, prevented many later complications such as common duct obstruction, pancreatitis, and acute cholecystitis. He compared the gall bladder containing gallstones to a time bomb set to do damage at an indeterminable time.

The chairman's address, presented by **Frederick A. Collier**, was one of the outstanding presentations of the meeting. Dr. Collier offered a critical analysis of his experiences with blood loss during surgery. He showed that blood loss is the greatest single factor in surgical shock, especially when associated with emotional exhaustion and surgical trauma. Emphasis was placed upon the fact that shock is much easier to prevent than to treat once it has developed, and the best way to prevent its development is to anticipate blood loss in advance and replace it as it is lost during the course of the operation, rather than using it to combat shock after it develops. Dr. Collier presented statistics showing the average blood loss in various types of surgical procedures, and called attention to the fact that blood loss in small patients is much more serious because of the relatively small total volume in such individuals. He showed that the usual clinical laboratory methods for estimating blood loss are unreliable, and that the only safe procedure is to accept the average blood loss as reported in the medical literature as a criteria as to the amount of blood which should be given during surgery. He pointed out that the average patient can manufacture only about 25 c.c. of blood daily, and that for this reason blood replacement will shorten convalescence and reduce complications and morbidity.

**Warren H. Cole** of Chicago stressed the potential dangers of nontoxic nodular goiter. He found that 16 per cent of the nontoxic nodular goiters were malignant. A correct preoperative diagnosis was made in only 20 per cent of these patients. Five-year cures were obtained in only 20 per cent of those patients in whom the goiter was diagnosed preoperatively, and in only 40 per cent of those in whom it was diagnosed at the time of operation, while 60 per cent of those in whom goiter

was not suspected until diagnosed microscopically were living and well five years after surgery. This is a strong argument for routine removal of all nontoxic adenomas.

**Forrest O. J. Young**, of Rochester, N. Y., reported his experiences with the use of plasma-thrombin as a "suture" material. He claimed three advantages for this material: the elimination of foreign body sutures, quicker wound healing, and its particular value in those patients who do not form their own fibrin. He stated that this material has been standardized and is nontoxic when used locally. He described in detail the procedure for its use.

**Frank E. Adair** presented a report of the clinical effects of surgical and x-ray castration in mammary cancer. He concluded that there is little or no choice between the two procedures. He observed that one-third of the surgical group had ovarian metastasis at the time of surgery, indicating a natural attempt at self-castration. He observed that the result of castration was spectacular in cases of breast malignancy in males.

**Willard H. Parsons**, Vicksburg, Miss., reported five cases of plasma cell mastitis. He commented upon the striking resemblance of this disease, which was first reported by Adair, to carcinoma of the breast, and discussed its differential diagnosis.

On the third day there was a joint meeting with the section on gastroenterology and proctology.

**A. H. Aaron**, Buffalo, N. Y., presented a paper dealing with the medical aspects of inflammatory lesions of the stomach and duodenum. Dr. Aaron called attention to the fact that peptic ulcer ranks high as a causative factor in the rejection of recruits for military service, and presented a plea for earlier diagnosis and a better plan for medical management of these ulcers.

**Frank H. Lahey** of Boston discussed the surgical aspect of peptic ulcer. He pointed out that all patients should receive adequate medical management and that only medical failures should be subjected to surgery. He discussed in some detail various technical problems in connection with the surgical treatment of this disease.

The second symposium of the day dealt with inflammatory lesions of the small intestines.

**Henry L. Bockus**, Philadelphia, Pa., discussed the medical aspect. He considered the problems presented by chronic stenosing regional enteritis. He feels that anxiety and emotional immaturity are etiologic factors, and thinks that food poisoning may play a part in the origin of this disease. He has found that the bowel lymphatic structures are involved early and always. Dr. Bockus is inclined to favor radical resection in extensive enteritis, but thinks that the exclusion operation is probably best in the average case. He has found that some of these conditions respond nicely to conservative medical management. He has found penicillin of no value, and has had no good results from vaccines and sera. He feels that the prognosis must be in doubt for many years, because remissions or recurrences may appear at any time.

**Henry W. Cave** of New York discussed the surgical aspect of segmental enteritis. Twenty-three patients with this disease were operated upon in the Roosevelt Hospital during the last ten years. Seven had appendectomy only. All of these did well and have had no more trouble. Dr. Cave feels that this indicates that the acute disease may subside without becoming chronic. He prefers ileocolostomy with exclusion in those cases requiring operation.

Inflammatory lesions of the colon was the final subject for discussion.



J. Arnold Bargaen, Rochester, Minn., discussed the medical aspect of this subject. Dr. Bargaen urged that ulcerative colitis be regarded as a syndrome rather than as a definite disease entity. He divided ulcerative colitis into the following etiologic groups: Streptococcic, tuberculosis, amoebic, lymphopathy venereum, and bacillary dysentery. Idiopathic colitis is reserved for a small group of non-specific cases of colitis of unknown cause and atypical clinical findings. Dr. Bargaen described in detail the differential diagnoses of these types of the disease.

Thomas E. Jones of Cleveland discussed the surgical aspects of inflammatory lesions of the colon. He called attention to the frequency of x-radiation stricture of the bowel, which is often overlooked as a diagnostic possibility. He considered ulcerative colitis and discussed the surgical complications, such as perforation, hemorrhage, pseudopolyposis, and the rare malignant degeneration. Diverticulosis was reviewed.

---

## TWENTY-FIFTH MEETING OF AMERICAN ASSOCIATION FOR THORACIC SURGERY

CHICAGO, ILL., MAY 5-6, 1944

F. C. FISHBACK, M.D., WASHINGTON, D. C.

**CORROSIVE Stricture of the Esophagus, Ralph Adams, Boston.**—Dr. Adams presented two cases, the first of mediastinitis, following esophagoscopy of the stricture and treated by mediastinotomy, with gastrostomy eight days later, and subsequently successfully dilated over a thread. The second case was that of a 29-year-old woman with a stricture of seven years' duration following ingestion of a corrosive substance, for whom life with a gastrostomy became intolerable. Through a right transpleural incision, a mid-esophageal, cordlike stricture, 2 cm. in length, was exposed, and with esophagoscopes in the stomach and mouth, a dilator was guided through the stricture, and then a string washed through. The esophagus was torn by the aspirator in the lower scope, but the rent was closed, and dilatations were begun thirty-five days after operation with good results. There are four common points of stricture formation, namely, the cricopharyngeal pinch-cock, the aortic crossing, the left primary bronchial crossing, and the cardia. He urged that the patient be made to swallow a thread promptly and that the thread be replaced from time to time to prevent breakage. Hydrostatic dilatation over a thread is safe, and retrograde dilatation is safer than through the mouth. Other treatments have been gastrostomy alone, resection of stricture with anterior thoracic esophagoplasty (cosmetically and functionally unsatisfactory), or resection of stricture with end-to-end anastomosis. The diagnosis of mediastinitis is based on the history of pain in the shoulder and/or upper abdomen, increased respiratory rate, fever and moderate leucocytosis, and the x-ray picture, showing restricted motion of the diaphragm and clouding of the inferior pulmonary angle. He warned against delay due to the seeming improvement eighteen to twenty-four hours after perforation.

**The Management of Benign Tumors of the Esophagus, Stuart Harrington, Rochester, Minn.**—Benign tumors of the esophagus are infrequent, present meager symptoms, often attaining considerable size without presenting severe symptoms, and are potentially malignant. They fall into two categories: (1) Mucosal, which are often pedunculated, usually fibrolipomas, and may regurgitate into the mouth if the stalk is long enough, and have been treated by snaring through the mouth or through cervical or transthoracic esophagotomy; (2) Extramucosal tumors are

---

Papers pertaining to war surgery and thymectomy have appeared in the August, 1944, issue of *The Journal of Thoracic Surgery*.

usually leiomyomas, do not obstruct, but may cause pain due to spasm. Surgery is usually not urgent, but when indicated is extensive.

**The Causes of Mortality Following Radical Resection of the Esophagus for Carcinoma, John Garlock, New York.**—Dr. Garlock reported sixty-six cases of tumors of the lower third of the esophagus (adenocarcinoma), with thirty-one patients operated upon and fifteen of them recovering, and sixty-five cases of tumors of the middle and upper third of the esophagus (squamous-cell carcinoma) with twenty-nine patients operated upon and sixteen recovering, presenting in all sixty operated cases with an operative mortality of 49 per cent. He emphasized: (1) The need for the utilization of a secure method of suturing the anastomosis; (2) Employment of a left transthoracic esophagogastric anastomosis for cancer of the lower half of the esophagus, with preliminary exploration and jejunostomy. He cautioned against gastrostomy because it immobilizes the stomach. (3) He advocated the Torek operation for the tumors of the middle and upper third. (4) He urged preservation of the blood supply of the stomach, and fixation of the intrathoracic portion of the stomach to the diaphragm. Nerve involvement indicates inoperability; furthermore, a very careful check should be made for nodes especially on the rectal shelf and in the supraclavicular region. The duration of dysphagia does not correlate with the degree of operability. The operative deaths were due to pulmonary and cerebral emboli, coronary disease, and pneumonia.

In the discussion of these papers, certain points were emphasized, namely, surgical excision of benign strictures was desirable where possible, and where the resected stricture was short, anastomosis was easy and fairly safe. Whether to bring up the stomach as such or as a preformed gastric tube, or to utilize the jejunum in reconstructing the esophagus were mentioned. The jejunum is more easily mobilized than the stomach and its blood supply is best six feet distal to the ligament of Treitz. The stomach, however, can be brought up as high as the superior mediastinum and its circulation is definitely superior to that of the jejunum. For benign strictures, operation is indicated only when the stricture is not dilatable.

**Current Observations on Thoracic Surgery in the Present War, Michael E. DeBakey, New Orleans.**—The mortality from chest wounds has fallen since the Civil War when it was 51.4 per cent, and from World War I, when it was 37 per cent, to about 27 per cent in World War II. In the present war, chest wounds comprise about 8 per cent of all wounds. Mortality and the incidence of infection are higher after wounds from shell fragments than from bullets. In previous wars, penetrating wounds exceeded nonpenetrating wounds, but in this war because of the utilization of mines, bombs, and torpedoes, nonpenetrating wounds of the chest are more frequent.

**War Wounds of the Chest Observed at the Thoracic Surgery Center, Walter Reed General Hospital, Major Brian Blades, Washington, D. C.**—All shell fragments should be removed if they are causing symptoms. The size and position of the fragments within the chest are factors for consideration. Some have to be removed because of the patient's knowledge of their presence and his ensuing fear and anxiety. Open thoracotomy is now safe, simply incising the lung and removing the foreign body. Lobectomy is not necessary or even desirable. Empyema has been exceedingly rare in Major Blades' experience. Draining sinuses are usually the result of a foreign body, necrosis of cartilage, or osteomyelitis of a rib. Of 107 patients with hemothorax, 77 were well by the time they arrived at Walter Reed, 24 were cured by aspiration, and only 6 required operation, namely, thoracotomy and decortication. Of these 6 none were very sick and none had a pneumothorax, and this apparently benign character of the injury was

probably responsible for the delay in aspiration. Blood left in the thorax may produce fibrothorax. Air replacement should be condemned and the aim of treatment should be prompt and complete re-expansion of the lung to obliterate the pleural space and abate the menace of empyema. When discharged, none of these patients had dyspnea or a reduced vital capacity. Chest wall pain sometimes followed and may have been due to pericostal sutures, which are not necessary.

**Trends and Practices in Thoracic Surgery in the Mediterranean Theatre, Colonel Edward D. Churchill, Consulting Surgeon Allied Force Medical Section.**—Attention is now being focused on the lung rather than the pleural space, as in the last war. Physiologic disturbances of intrathoracic physiology are corrected immediately, with reduction in shock, infection, and morbidity. Hemorrhage from the chest wall into the pleural space is aspirated and used for autotransfusion. Sucking wounds of the chest wall are no longer sutured, but are closed with tight petrolatum gauze compresses. Tension pneumothoraces are rare; the air is vented. A catheter with a flutter valve may be used for the tension pneumothorax. "Wet lung" is treated by bronchial aspirations, oxygen, and novocain block of the intercostal spaces to release bronchospasm and permit painless coughing. Thoracotomy is rarely done. There remains a divergence of opinion as to the indication for thoracotomy; it should be done only with a precise aim in view, since it may delay re-expansion of the lung. Thoracotomy done five to ten days after injury may prevent infection. Hemothorax should be treated by repeated aspirations but after the fourth week they tend to become static. High explosive fragments produce continued bleeding with deposition of plasma and red blood cells in the pleural space.

These cases should be appraised by the fifth or sixth week and if the fibrin envelop persists, thoracotomy and decortication should be done to prevent fibrothorax. Air replacement is not done except for continuing hemorrhage and then thoracotomy is preferable. Patients with asymptomatic foreign bodies are returned to duty; if the foreign body produces dyspnea, it is removed.

Discussors brought out the facts that if air replacement were done at all, it should be done within the first twelve hours; that when the bleeding was from the chest wall, air replacement was obviously useless; that the aim should be complete aspiration and early re-expansion of the lung; that empyema does not occur if the chest is left dry; that if blood is left behind, fibrothorax will ensue and the patient will become a respiratory cripple. The excellence of the care of the wounded men before being brought to the army thoracic centers was commented on.

**Difficulties in the Differential Diagnosis of Bronchogenic Carcinoma, R. G. Bloch, and W. E. Adams, Chicago.**—Extensive x-ray surveys have revealed an increasing number of unsuspected intrathoracic neoplasms. In 15,000 x-ray examinations at the University of Chicago Clinic, 91 neoplasms were discovered: 34 (or 37 per cent) were metastatic carcinoma, 25 (or 27 per cent) were primary pulmonary carcinoma, 19 (or 21 per cent) were lymphomas, 5 were sarcomas, 1 dermoid, 1 neurofibroma, and 1 hemangioma (last group, 14 per cent). Thirteen per cent of the early bronchogenic carcinomas were peripheral and beyond the reach of the bronchoscope for diagnosis.

**Bronchial Adenoma, C. L. Jackson, Philadelphia.**—Dr. Jackson presented twenty bronchial adenomas. Fourteen occurred in women (70 per cent). The age incidence ranged from 13 to 52 years, with predominance in the second and third decades. Hemoptysis and cough were the common symptoms. All diagnoses were based on bronchoscopic biopsies. The histologic criteria were (1) epithelial proliferation with a peculiar stroma, (2) "packed" cells with pyknotic nuclei, (3) absence of mitotic figures, (4) a resemblance to fetal lung, (5) glandular pattern not always evident. These tumors at times seem to regress; incomplete re-

moval does not accelerate their growth rate, and malignant change is uncommon. Seventeen of these patients were treated bronchoscopically, the tumor being removed with forceps or by coagulation. Three were treated by pulmonary resection.

**The Problem of So-called Adenoma of the Bronchus, Evarts Graham, and N. A. Womack, St. Louis.**—The term "adenoma" connotes a benign tumor. Dr. Graham recalled his earlier paper on the subject in which he stated that these tumors were potentially malignant, that they were derived from mesoblastic as well as epithelial elements, that they resembled fetal developmental abnormalities, and possessed invasive properties. Other authors had also reported such tumors undergoing malignant degeneration. Brunn and Goldman had suggested in 1940 that these bronchial tumors which became malignant be termed "papilloma" instead of adenoma. These tumors do not ulcerate; their cell structure is characterized by pleomorphism and they resemble persistent fetal lung buds. Congenital anomalies tend to become malignant and such anomalies are associated with bronchial adenomas. That only a few have been found at necropsy may be due to their having replaced their adenomatous characteristics with those of malignancy. They usually lie close to the carina, in a main stem bronchus. Radical resection was advised. Lobectomy was usually impossible in light of their common location. Bronchoscopic removal has been done on some, but with worry and concern on the part of the surgeon as to the ultimate fate of the patient.

In the discussion, Harold Brunn advised bronchoscopic removal before lung resection, and added that when death occurred it was not due to the tumor, but to infection distal to the tumor. Ralph Adams cited 17 adenomas at the Massachusetts General Hospital, out of a series of 174 lung tumors; 5 of these were removed bronchoscopically, 1 was found at autopsy, and 11 were treated by pulmonary resection with but 1 death. In contrast to these figures, he said that out of the 28 patients with bronchogenic carcinomas resected, only 3 (11 per cent) were living. Planography has been helpful in demonstrating the invasiveness of these tumors. John Alexander (Ann Arbor) said that these adenomas are grade 1 carcinomas. In their series at the University of Michigan, they have had 13 such cases, two of which showed metastases. In one instance, a medullary carcinoma, grade 3, was found in a metastatic gland. Dr. Jackson closed, saying that these adenomas arise chiefly at bronchial spurs; that the sequelae of bronchial obstruction were the real cause of trouble; that they show no inherent tendency to malignancy, and that accurate pathologic diagnosis is essential. Cell structure may and does vary in different parts of the same tumor. Dr. Graham closed his remarks by saying that an adenoma might metastasize to a lymph gland without being malignant; but that while it shows no mitoses, and grows slowly, it is invasive, and potentially malignant, comparing it with a mixed tumor of the parotid which might exist twenty years before undergoing malignant change. He cited eight cases of adenomas which showed regional or distant metastases.

**An Attempt to Evaluate the Effects of Thymectomy in the Treatment of Myasthenia Gravis, Alfred Blalock, Baltimore.**—The knowledge of the relationship of the thymus to myasthenia gravis is meager and vague. Thymic tumors have been found in about one-half the cases of myasthenia gravis. The prostigmine test is important in diagnosis; the optimum dose must be determined before operation. Patients do have spontaneous remissions, making it difficult to evaluate the benefits of the operation. The rationale of the operation is based on the cure of myasthenia gravis in 1936 by the removal of a thymic tumor. It was subsequently tried where no tumor was present. He advised the use of an intratracheal catheter, very little ether, local anesthesia, and a median sternotomy. Of 20 patients operated on, 4 have died, 3 showed little or no improvement, 5 moderate improvement, 5 considerable improvement, and 3 may be regarded as

well. The more severe the myasthenia gravis, the greater likelihood of benefit from thymectomy. If a thymic tumor is present, it should be removed. Thymectomy is indicated if the patient is disabled, even though there is considerable risk. Prior to the use of prostigmine, 70 to 80 per cent died; 22 out of 100 patients died, when treated with prostigmine. There is no way to predict the improvement to be expected from the operation, except that the shorter the pre-operative disability, the better the results have been. X-ray treatment was useless in the absence of a thymic tumor. It would appear that other factors are involved besides the thymus.

**Indications for Pericardiotomy With Special Reference to Exposure of the Infected Patent Ductus Arteriosus, Harold Neuhof, New York.**—Dr. Neuhof advocated a transpleural pericardiotomy as simpler and safer, except in the presence of infection. Aside from the usual indications, he advocated its use for obscure manifestations suggesting low-grade pericardial infection, for determining the existence of any residual after drainage for suppurative pericarditis, also occasionally to discover the extent of hilar invasion in carcinoma of the lung and to decompress tamponade-producing effusions. More particularly the transpleural approach offers better exposure for ligation of the patent ductus arteriosus in cases of bacterial endocarditis. In the discussion, **Stuart Harrington** also endorsed the posterolateral approach, saying that it gave better exposure and greater ease in controlling possible hemorrhage, should it occur. **J. C. Jones** did not recommend opening the pericardium in ligating the patent ductus because the pericardial fluid obscures the operative field; he said also that cutting the fibrous attachments to the aorta lengthens the ductus and facilitates its ligation.

**Arteriovenous Fistula of the Lung, John C. Jones, Los Angeles.**—Arteriovenous fistula of the lung is a rare lesion which presents a clear-cut clinical entity, consisting of cyanosis, clubbing of the fingers and toes, polycythemia, a normal heart, and increased blood volume with decreased oxygen saturation. Planography is helpful when a bruit is absent. He presented a case of a 24-year-old white woman with a red count of  $6\frac{1}{2}$  to  $7\frac{1}{2}$  million, hemoglobin 130 per cent, blood pressure 112/94, clubbing of the fingers, a murmur over the tumor mass, and x-ray pictures showing "tumor of the right lung" and "dilated vessels to middle lobe." A pneumothorax of five months' duration did not collapse the tumor, and did cause dyspnea and mediastinal herniation. When pneumonectomy was done, no transfusion was given because of the polycythemia.

In the discussion, **Robert M. Janes** reported three cases, one of which was bilateral, with operation and recovery. Ligation of the branch of the pulmonary artery to the involved lobe was suggested, but **Dr. Jones** thought this would be ineffectual in controlling the shunt.

**Hydatid Disease of the Lung, Louis R. Davidson, New York.**—The presence of our troops in countries where hydatid disease of the lung is prevalent is going to account in the future for its more frequent occurrence in this country. Although echinococcus infestation involves the liver in from 75 to 90 per cent of the cases, cyst formation in the lung occurs in about 10 per cent. Diagnosis is based on an eosinophilia (usually over 4 per cent), complement fixation test (unreliable, giving false positives), skin test (Casoni), and sputum examination for hooklets and scolices. The cysts should not be punctured for diagnosis. These lung cysts have three layers, an inner, germinal layer, a middle layer or laminated membrane, and an outer layer or adventitia, representing a connective tissue reaction. In x-ray, these cysts appear round, homogeneous and sharply outlined, and often a crescentic space appears within the cyst, which may be pathognomonic. Treatment consists of a two-stage thoracotomy, eradication of the cyst at the second stage,

and treating the cyst bed with 2 per cent formalin. In the discussion, Leo Eloesser suggested that lobectomy should shorten convalescence and reduce possible complications.

**Studies of the Pathogenesis, Dynamics and Closure of Tension Cavities, H. M. Riggins, and R. P. Gearhart, New York.**—Tuberculous cavities result from liquefaction and expulsion of caseous material. All bronchi communicating with cavities are diseased. Behavior of cavities depends on whether the bronchus is open or closed. Rapid enlargement of tension cavities had often been observed without corresponding caseation and liquefaction of lung tissue. Clinically, tension cavities exhibit wheezing, fever, and varying amounts of sputum; symptoms are often aggravated at the menses due to bronchial swelling. By means of transthoracic needling, done only through an obliterated pleural space, it was found that in a cavity with a closed bronchus, there was a positive pressure; when more air is injected, the pressure rises and remains elevated, and when air is aspirated, the pressure remains negative. Gas analysis showed a low oxygen content with a closed bronchus, and atmospheric oxygen when the bronchus was open. The tubercle bacillus was always present in cavities; the presence of another organism was variable. Tension cavities behave unpredictably.

**The Determination and Treatment of Pressure Cavities in Pulmonary Tuberculosis, A. M. Vineberg, and W. E. Kunstler, Montreal.**—Vineberg and Kunstler found that a large percentage of tuberculous cavities were "tension" cavities and were rarely closed by thoracoplasty. The detection of these cavities can only be accomplished by needling and recording intracavitary pressures. Intracavitary suction drainage will reduce such cavities to the size of the catheter, but permanent closure requires partial thoracoplasty. Negative pressure cavities close readily with thoracoplasty. Suction drainage and thoracoplasty afford the ideal treatment for closure of tension cavities. With giant cavities, they advocated an anterior thoracoplasty prior to suction drainage.

**An Evaluation of the Monaldi Suction Drainage of Tuberculous Pulmonary Cavities, J. R. Head, Chicago.**—The Monaldi procedure may be useful in both tension and nontension cavities. Head employed it in patients with low vital capacity and to reduce the size of extremely large cavities. It should not be used if other accepted methods of treatment are applicable. Under local anesthesia, he makes a small anterior intercostal incision, puts in a pack, closes it, and later after the formation of adhesions, inserts a catheter.

In discussing this group of papers, John Alexander said that the Monaldi procedure rarely closes a cavity and that a large percentage of cavities are *not* tension cavities. Thoracoplasty *does* close many tension cavities. The present tendency is to fewer rib thoracoplasties with dropping in of the scapula, to preserve as much sound lung as possible. The abolition of the inspiratory excursion in the collapsed lung removes the cavity distending factor. E. J. O'Brien stated that from 80 to 90 per cent of all cavities were closed by pneumothorax or thoracoplasty. If a cavity required drainage, he preferred open drainage to the Monaldi method. Leo Eloesser said, "This discussion proves that we don't know what we're doing when we operate on tuberculosis." He preferred the term "blocked cavity" to "tension cavity," but would compromise on "insufflation cavity." Cavities, he said, were caused by two factors, (1) insufflation, which is intermittent, part-time, and pertains only to round cavities, and (2) extrinsic factors, such as caliber of the communicating bronchus, the character of the surrounding lung, and extremely involved aerodynamic factors. Insufflation cavities demonstrate that positive pressure exceeds negative pressure within them most of the time. In closing, Dr. Riggins emphasized that pneumothorax fails in positive pressure cavities. Dr. Vineberg said that in

Canada, 30 per cent of cavities persist after thoracoplasty and that cavity drainage reduces the amount of surgery and avoids the sacrifice of good lung for adequate collapse.

**Pulmonary Resection in the Treatment of Tuberculosis: Introductory Remarks, F. S. Dolley, Los Angeles.**—Dr. Dolley emphasized the need for precise indications and criteria of satisfactory results. In general, lung resections for tuberculosis have gone too far, often because of the difficulty in selecting the correct cases. Cases suitable for less radical surgery should be excluded. The usual complications after resection are extension and/or contralateral spread, empyema, and bronchial fistula with positive sputum.

**Total and Partial Pneumonectomy in the Treatment of Pulmonary Tuberculosis, E. M. Janes, Toronto.**—Dr. Janes reported 15 cases of pneumonectomy, with 48 per cent mortality, done because of bronchial stenosis, and 16 partial pneumonectomies (7 in upper lobes and 9 in lower lobes) with 25 per cent mortality. These latter were unusually difficult when the cavity was close to a fissure. He employed a posterolateral approach and individual ligation technique; and closure was with pericostal sutures because they enhanced the comfort of the patient by immobilizing the ribs adjacent to the operative field.

**Lobectomy in Pulmonary Tuberculosis, H. C. Maier, New York.**—Dr. Maier reported 16 cases of lobectomy done in the past one and one-half years, and excluded all cases in which previous operations had been done, as well as those in which an accidental finding of tuberculosis occurred. The risk is not so great when individual ligation technique is used, along with improved anesthesia and appropriate pre- and postoperative care. His indications were: (1) in certain cases, in anticipation that collapse therapy might fail, (2) in some where there was no definite contraindication to thoracoplasty, (3) the lesion situated at a site, unfavorable for collapse therapy, (4) tension cavities where pneumothorax had failed, (5) bronchial tuberculosis, (6) lower lobe cavities, (7) extensive cavitation, limited to a single lobe, (8) shrunk lobe, (9) unilateral disease in a young patient where thoracoplasty might give poor result. He felt that modern anesthesia should prevent contralateral spread. He used a posterolateral incision. There were 12 cases of upper and middle lobe lobectomy, and 4 lower lobe operations. Dissection from the chest wall may be very difficult; in fact may cause abandonment of the operation. He covered the bronchial stump with a pleural flap. Completion of fissures was often difficult. Time was saved by working slowly, the average time of operation being five hours. The average fall in blood pressure was only 13 mm. mercury (the greatest being only 25 mm.), and transfusions of 1,000 c.c. of blood were given during operation. Drainage was carried out for twenty-four to forty-eight hours. Ten patients had uneventful postoperative courses; 3 were uneventful except for increased density in the opposite lung which cleared later; 1 had an apical empyema (staphylococcus); 1 had a tuberculous empyema with bronchial fistula and will require a later thoracoplasty; and finally 1 death occurred a month after operation from extensive spread to the opposite lung. Of the 15 survivors, 12 had negative sputa, 2 had positive sputa, and 1 is too recent to evaluate. Thoracoplasty was done later in 1 case.

**Primary Upper Lobectomy Versus Modern Selective Thoracoplasty in the Treatment of Tuberculosis, J. M. Chamberlain, Oneonta, N. Y.**—Years ago, the aim in treatment of tuberculosis was apparently obesity; later it became sputum conversion (bacteriologic cure), and now it is sputum conversion plus rehabilitation of the patient. Endobronchial tuberculosis is always present when there is a cavity. With bronchial obstruction, there may be emphysema, atelectasis, and tension cavities. Control of the parenchymal focus controls the endobronchial tuberculosis. The degree of emphysema is proportional to the size and extent of

the lesion. The status of the remaining lung tissue is quite as important as sputum conversion. The functioning alveolar units and the bellows action of the chest must be preserved, and if lobectomy produces a compensatory emphysema, it harms the remaining lung. The principles of treatment are: (1) drainage, (2) immobility, (3) relaxation, (4) compression, and (5) resection. Thoracoplasty satisfies these criteria in the following order, namely, No. 3, 4, 1 and 2. Respiratory function after thoracoplasty may be unchanged, increased, or decreased. Upper lobectomy to control a major focus produces overdistention of the remaining lung, especially the alveoli, and is less physiologic than selective thoracoplasty, which preserves the oxygenating function of the remaining lung tissue by preventing alveolar distention. Since lobectomy produces alveolar distention and poor function, it should be used secondarily, in the event of failure of thoracoplasty. The following tabulation represents some of the results quoted by those discussing these papers:

PNEUMONEC- TOMY	LOBECTOMY	TOTAL	DEAD	DOCTOR
12	9	21	6	C. P. Bailey, Philadelphia
?	?	35	20	R. H. Sweet, Boston
		97	21 (22%)	Wilson, Boston
10	3	11	Not given	J. R. Davidson, New York
3	5	8	2	S. O. Freedlander, Cleveland

Dr. Sweet's figures were from the Massachusetts General Hospital. Dr. Wilson was quoting Dr. Overholt's results. If one is able to clamp the bronchus first, it may prevent contralateral spread. E. J. O'Brien conceded that while lung resection is less hazardous than formerly, it is responsible for spreads and empyemas. He felt that lung resections do produce compensatory emphysema, while thoracoplasty preserves good lung tissue. Bronchostenosis is not a contraindication to thoracoplasty since such stenoses may be dilated before and after thoracoplasty. John Alexander said of the newer procedures, such as the Semb apicolysis (often complicated by subscapular infection), extrapleural pneumothorax, Monaldi and lung resection, that each may have its place, but that they should not be used where thoracoplasty would be effective. In case of doubt, it is best to err on the side of conventional collapse therapy because the risk is less. The newer procedures may be done successfully and still leave a positive sputum. The risk of a spread after lung resection is still considerable. John Strieder summed up the indications for lobectomy as (1) tuberculoma, (2) tuberculous bronchiectasis, (3) tension cavities, and (4) bronchostenotic lesions. S. O. Freedlander gave an additional indication for lobectomy, namely, compression of an upper lobe bronchus by extrabronchial tuberculous glands. In closing, Dr. Dolley asked the personal question as to whether any of the audience would have a lung resection for tuberculosis, and then summed up the indications as he saw them, namely (1) cavities near the mediastinum (unlikely to be closed by thoracoplasty), (2) tension cavities after thoracoplasty, and (3) progressive bronchostenosis. Dr. Janes wondered whether the effect of overdistention of the remaining alveoli was as bad as depicted. Dr. Maier said that after lobectomy for bronchiectasis, there is little change in lung function; and also that the immediate postoperative pleuritic reaction masks true lung function. Dr. Chamberlain asked us to focus our attention on the remaining lung, and emphasized the fact that emphysematous lung tissue was functionless even though it appeared normal by x-ray. He said that bronchial peristalsis is lost after upper lobectomy and that there is decreased bronchial motility after any lung resection, making tuberculous spreads easier.



**The Use of Whole Blood Transfusion in Resections of the Lung, W. E. Adams, and T. F. Thornton, Jr., Chicago.**—Large citrated blood transfusions may cause citrate intoxication. Referring to John Gibbon's paper on fatal pulmonary edema at the Toronto meeting, produced by very large and rapid transfusions after bilateral lobectomy in cats, Dr. Adams said that the possibility of pulmonary edema depended on (1) the amount of lung resected, (2) the amount of blood given (it never occurred with 15 c.c. per kilogram, the equivalent of one liter per 70 kg. in man), (3) the rate of administration, and (4) overtransfusion. Blood may be given to replace any operative loss without producing pulmonary edema. Blood should be replaced as it is lost and not after first giving plasma or glucose. Blood loss is usually underestimated; it will usually average 1,500 c.c. for lobectomy or pneumonectomy.

**Studies in Oleothorax, P. D. Crimm, Evansville, Ind.**—Tuberculous empyema is the result of rupture of subpleural tuberculous focus by ulceration. The infected pleura cannot be chemically disinfected without doing more harm than good. Peanut oil and cod liver oil are irritating; they inhibit the growth of the tubercle bacillus and produce exudates that seal the ruptured foci. The oil must cover the entire pleura until pleural thickening occurs. These oils stimulate an obliterative pleuritis. Should the lung fail to re-expand, a less extensive Schede will be required. By the use of oleothorax, aspirations are less frequent.

## Notices

---

### TO AID WAR EFFORT, AMERICAN COLLEGE OF SURGEONS CANCELS 1944 CLINICAL CONGRESS

The American College of Surgeons, upon action of its Board of Regents, has canceled its Annual Clinical Congress because of the acute war situation that has developed, involving greater demands than at any time in the past upon our transportation systems for the carrying of wounded military personnel, troops, and war materiel. The Congress was to have been held in Chicago, Ill., Oct. 24 to 27.

Dr. Irvin Abell of Louisville, Ky., chairman of the Board of Regents, in making the announcement, said that this action was taken after consultation with officials in Washington, D. C. Some of the replies which were received from these officials read in part as follows:

From Major General Norman T. Kirk, Surgeon General, United States Army:

Naturally, we all like these meetings to be held and to attend them. However, from an official standpoint I must say we are needing more and more railroad transportation to move our battle casualties from the ports to our hospitals. And there are still many troops in the United States who require railroad transportation to ports in order to get them overseas. In addition, difficulty is being experienced in obtaining the necessary materiel to continue the battle. This means transportation for the raw materials that go into munitions and the shipping of these munitions to the ports after they are fabricated. Each month the need for this material overseas is increasing rather than diminishing.

The war is far from won and I think we should all consider the war effort rather than the satisfaction of our individual desires. That should give us the answer. After seeing the bomb craters and destroyed homes, factories, and transportation facilities in Europe, I am not surprised that this nation feels it is far removed from war and that the war is about over. It isn't.

From R. H. Clare, assistant director, passenger section, division of traffic movement, Office of Defense Transportation:

This office cannot attempt to evaluate the importance or the essentiality of any particular meeting. We have attempted to portray clearly the present critical transportation situation. The transportation requirements of the Armed Forces are not at present being entirely satisfied. At the same time, soldiers and sailors on leave from duty overseas are unable to secure Pullman accommodations to their homes and frequently have to stand in coaches for considerable distances. The responsibility, therefore, rests upon the officers of your organization to determine if, in the light of these conditions, you should go through with your Chicago meeting.

I believe you will agree that the Office of Defense Transportation cannot attempt to make this decision for you. We assure you that there is an urgent need for the curtailment of convention travel in order to clear the transportation channels of the country for the movement of military and essential civilian travel. We, therefore, ask for your serious consideration of our appeal in the light of this situation.

Feeling that the many factors in favor of holding the Clinical Congress, however important, are less vital than the assurance of adequate transportation and the best medical care for the wounded, as well as the clearance of transportation facilities as far as possible for the conveying of troops and war materiel, the American College of Surgeons willingly cancels, for the third successive year, its annual meeting, in order to aid the war effort. The Regents recognize that there is a great burden on the members of the surgical profession in their local communities as the result of the large proportion of the profession which is serving with the Armed Forces. They also take cognizance of the desire of the profession to do nothing which would interfere with the successful prosecution of the war program, such as would be caused by the temporary absence of its members from duties during the period of the Congress. More than 3,000 surgeons and some 2,000 hospital representatives usually attend the Clinical Congress.

At the annual meeting of the Board of Regents which will be held later in the year, fellowship in the College will be conferred *in absentia* on the class of initiates of 1944, as there will be no convocation exercises. At the same time the list of hospitals, cancer clinics, medical services in industry, hospitals conducting programs of graduate training in surgery, and medical motion pictures, that meet the College standards, will be approved and later published.

All present officers, regents, governors, and standing committees will continue in office.

War conditions permitting, the Clinical Congress will be held in the fall of 1945.

---

## THE ASSOCIATION OF MILITARY SURGEONS OF THE UNITED STATES

Office of the Chairman of the Convention and Program Committees,  
Governors Island, New York, N. Y.

Addresses by the nation's three surgeons general, the chief of the Veterans Administration, the commanding general of the Second Service Command, and New York City's mayor will highlight the fifty-second annual meeting of the Association of Military Surgeons of the United States at the Hotel Pennsylvania, New York, N. Y., Nov. 2 to 4, 1944.

Other features of the meeting, which is being arranged under the direction of Colonel Lucius A. Salisbury, association president, and Colonel Charles M. Walson, chairman of the convention and program committees, will be forum lectures, discussion panels, military and commercial scientific exhibits, and medical motion pictures.

Expected to participate in the forums and discussions are: Major General Norman T. Kirk, Surgeon General, U. S. Army; Admiral Ross T. McIntire, Surgeon General, U. S. Navy; Surgeon General Thomas F. Parran, U. S. Public Health Service; Major General David D. W. Grant; Rear Admiral Luther Sheldon; Major General G. Brock Chisholm of Canada; Brigadier Generals Frank T. Hines, James S. Simmons, Charles C. Hillman, Raymond W. Bliss, Fred W. Rankin, Hugh J. Morgan, and Stanhope Bayne-Jones; Dr. Warren F. Draper, U. S. Public Health Service; Dr. Chester Keefer of Boston; and Dr. R. E. Dyer, National Institute of Health.

Forum lectures will cover war surgery, chemotherapy, communicable diseases, neuropsychiatry, medical problems in theaters of operation, dental rehabilitation, and equine encephalitis.

Topics for discussion panels, which will be integrated with the lectures, are: War Wounds, Burns, and Fractures, Neuropsychiatric Problems, Treatment and Prevention of Venereal Diseases, Penicillin and Sulfonamide Therapy, Orthopedic and Reconstruction Therapy, Neurosurgical Problems, Tropical Diseases in the Army and Navy, and Aviation Medicine.

Separate discussions have also been arranged for Dental, Veterinary, Sanitary and Medical Administrative Corps officers.

Colonel Frederick H. Foucar, of the Second Service Command Laboratory, is chairman of the committee arranging the scientific exhibits, which will include material from Army, Navy, and Veterans Hospitals, the Carlisle Barracks Medical Field Training School, many medical depots, and the Office of the Army Surgeon General. All available space for the technical exhibits of commercial firms was disposed of months ago.



Major General Norman T. Kirk, Surgeon General of the Army and honorary chairman of the fifty-second annual meeting of the Association of Military Surgeons, which will be held at the Hotel Pennsylvania, New York, N. Y., Nov. 2 to 4, 1944, inclusive. (U. S. Army Medical Museum)

The annual banquet, which is to be addressed by a prominent speaker representing the Army, will be held November 3, and an entertainment is planned for the night of November 2. The banquet speech and the speeches of the Surgeons General and the Veterans Administrator will be broadcast nationally, while "spot" broadcasts will probably be made by several of the principal forum speakers.

Other committee chairmen for the meeting are: Brigadier General Ralph G. DeVoe, M.C., reception; Lieutenant Colonel Howard F. Baer, Sn.C., entertainment; Lieutenant Colonel Ralph E. Ladue, A.U.S., reservations; Colonel George W. Hinman, Jr., public relations; Mrs. Norman T. Kirk (honorary) and Mrs. Lucius A. Salisbury, women's hostess.

The registration desk will open November 1. Lieutenant Colonel R. E. Ladue, 52 Broadway, New York 4, N. Y. (HA. 2-5200), should be notified of any difficulty encountered in securing rooms through the Hotel Pennsylvania.

## Book Reviews

---

**Physical Foundations of Radiology.** By Otto Glasser, Ph.D., Professor of Biophysics and Head of Department of Biophysics, Cleveland Clinic Foundation, Cleveland, Ohio; Edith H. Quimby, Sc.D., Associate Professor of Radiology (Physics), College of Physicians and Surgeons, Columbia University, New York, N. Y.; Lauriston S. Taylor, Ph.D., Chief of X-Ray Section, National Bureau of Standards, Washington, D. C.; and J. L. Weatherwax, M.A., Philadelphia General Hospital and Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pa. Pp. 426. New York, 1944, Paul B. Hoeber, Inc.

Presented in a readable, easily understood, concise form, the general principles underlying the use of radiation for medical purposes are here set forth.

This small volume contains a brief description of the history of radiology, of the nature of radiation, the character of x-ray apparatus, and means of production of x-rays. The application of roentgen rays to diagnosis and therapy is briefly discussed. The methods of measurement, both of x-rays and radium, are elaborated. The theories of radioactivity and the uses of radium are briefly presented. Protective measures against the deleterious effects of radiation are discussed in some detail. The authors are all pre-eminent in their respective fields. The book can be highly recommended to anyone using roentgen or radium radiation as a well-written authoritative introduction to the subject.

# SURGERY

VOL. 16

NOVEMBER, 1944

No. 5

## Original Communications

### *Symposium on Surgical Lesions of the Thyroid*

#### DIFFUSE AND ADENOMATOUS GOITER AND GOITER INDUCED BY VARIOUS AGENTS

ALBERT C. BRODERS, M.D., AND EDITH M. PARKHILL, M.D.  
ROCHESTER, MINN.

*(From the Division of Surgical Pathology, Mayo Clinic)*

GOITER, like many other pathologic processes, has been thoroughly described by numerous writers. In view of the brevity of this paper, however, we deem it pertinent to draw on the literature in a more or less limited manner and to utilize for the most part our own experience in the presentation of the pathology of diffuse colloid goiter, diffuse hypertrophic parenchymatous or exophthalmic goiter, and hypertrophic parenchymatous or exophthalmic goiter with adenomas and adenomatous goiter with and without intra-adenomatous parenchymatous hypertrophy. The diffuse hypertrophic parenchymatous or exophthalmic goiter and hypertrophic parenchymatous or exophthalmic goiter with adenomas have been variously designated Parry's disease, Flajani's disease, Basedow's disease, and Graves' disease. In addition to the foregoing goiters, we shall call attention to certain other goiters that have been incidental findings in man and deliberately induced in experimental animals by various agents.

#### DIFFUSE COLLOID GOITER

The diffuse colloid goiter, which used to be observed frequently from prepuberty to late adolescence, according to Haines<sup>1</sup> is rarely observed today by the clinician. Furthermore, it is almost never seen by the surgical pathologist. This type of goiter, as its name implies, presents itself macroscopically on section as a vesicular, usually soft,

Received for publication, July 10, 1944.

sticky, glistening colloid mass (Fig. 1). On microscopic examination the goiter consists of follicles or vesicles of various sizes lined with cuboidal or flat epithelium and distended with a pale eosin-staining (acidophilic) thin colloid (Fig. 2).



Fig. 1.—Diffuse colloid goiter showing vesicles filled with colloid.



Fig. 2.—Diffuse colloid goiter shown in Fig. 1, follicles are lined for the most part with flattened epithelium and contain thin pale-staining acidophilic colloid (hematoxylin and eosin  $\times 75$ ).

Hertzler<sup>2</sup> attached physiologic, clinical, and pathologic significance to the staining properties of colloid. He pointed out that normal colloid is acidophilic and stains pale pink with eosin, that if the stain is less intense than normal, the colloid is thin, and that pale-staining colloid is usually associated with cellular hyperplasia, is most marked in toxic goiters, and is to a degree a measure of toxicity. He further stated that thick colloid is indicated when the staining with eosin is more intense than normal, that it is commonly present in old goiters especially when there is degeneration of the connective tissue, and



Fig. 3.—Diffuse nonadenomatous exophthalmic goiter in which the normal contour of the thyroid is preserved (thyroid-shaped goiter of MacCarty).

that colloid which stains deeply with eosin is in the last stage of usefulness. The colloid that stains with hematoxylin, or basophilic colloid, he considered pathologic. He stated that basophilic colloid is associated with an atrophic and degenerated epithelium and that on the whole it is more pronounced in old goiters that are the seat of degenerative changes and in goiters associated with heart failure. These observations suggest the possibility that colloid of this type is representative of a substance which affects adversely the heart function and that those acini which contain basophilic colloid are permanently functionless.



DIFFUSE HYPERTROPHIC PARENCHYMATOUS THYROID OR  
EXOPTHALMIC GOITER

Before H. S. Plummer<sup>3</sup> instituted the preoperative administration of compound solution of iodine to patients with exophthalmic goiter, the diffuse nonnodular and nonadenomatous hypertrophic parenchymatous goiter as seen by the surgical pathologist was a light brownish to reddish, fairly fine-grained, firm gland, regular in outline and often comparable in appearance to veal or beefsteak. Because its contour remains for the most part like that of the normal gland, MacCarty<sup>4, 5</sup> termed it a "thyroid-shaped goiter" (Fig. 3). Colloid, although present in all exophthalmic goiters prior to the universal preoperative



Fig. 4—Diffuse nonadenomatous exophthalmic goiter showing follicles of various shapes and sizes lined with epithelium that ranges from cuboidal to high columnar and containing a small amount of thin pale-staining acidophilic colloid (hematoxylin and eosin  $\times 125$ ).

administration of compound solution of iodine, was not an outstanding feature at that time. The usual microscopic picture was that of round, oval, or irregular follicles lined with epithelium which ranged in form from cuboidal to high columnar. The follicles also were characterized to a large extent by a papillary infolding of the epithelium and contained a small to a moderate amount of colloid of varying density

(Fig. 4). It was rather unusual to see an exophthalmic goiter of which the colloid content was comparable to that of a colloid goiter.

Since the advent of administration of compound solution of iodine, the typical meaty exophthalmic goiter is seen much less frequently and has for the most part been replaced by a gland comparable to a colloid goiter, although smaller. The change in the exophthalmic goiter is undoubtedly attributable to administration of the compound solution of iodine. Following administration of compound solution of iodine, the epithelium changes from columnar to a low cuboidal or flat type and the acini dilate or at least have larger lumina, and their colloidal content increases (Fig. 5). This increase in the size of the



Fig. 5.—Diffuse nonadenomatous exophthalmic goiter showing the effect of the administration of compound solution of iodine. The cells lining the follicles are for the most part flat or low cuboidal with some low columnar epithelium still present. The colloid dropped out in preparation of the section (hematoxylin and eosin  $\times 100$ ).

lumina is probably the result of the diminution in the size of the cells. Some exophthalmic goiters on the other hand are more or less resistant to the changes that usually take place after administration of compound solution of iodine.

#### HYPERTROPHIC PARENCHYMATOUS THYROID OR EXOPHTHALMIC GOITER WITH ADENOMAS

The adenomas (Fig. 6) in hypertrophic parenchymatous thyroid or exophthalmic goiter may have follicles lined with columnar epithelium

like those seen in the extra-adenomatous portions of the goiter and, in addition, other follicles lined with cuboidal or flattened epithelium and more or less filled with colloid. Fetal acini or small undeveloped follicles lined with cuboidal epithelium and containing little or no colloid also may be present. The nodules sometimes observed in hypertrophic parenchymatous thyroid or exophthalmic goiters with or without adenomas differ from the true adenomas of exophthalmic goiter in that



Fig. 6.—Multiple adenomas in a hypertrophic parenchymatous thyroid or exophthalmic goiter.

they are not encapsulated, rarely contain true fetal acini, and under the microscope usually resemble the extranodular part of the goiter. In other words the nodules are to a large extent comparable to the nodules observed in hyperplasia of the prostate gland.

In all hypertrophic parenchymatous thyroids or exophthalmic goiters, that is, in the diffuse nonnodular, the nodular, and the adenomatous types, varying degrees of chronic thyroiditis may be present. The

chronic thyroiditis in these goiters is characterized by fibrosis and lymphocytic infiltration of the interfollicular tissue, with or without formation of germ centers. This inflammatory reaction is probably attributable not to bacterial activity but to toxic products of the goiter. To some extent this form of thyroiditis may be activated by compound solution of iodine, as it has been more in evidence since the therapeutic use of compound solution of iodine began.



Fig. 7.—Partially degenerated, well-encapsulated adenoma of the thyroid.

Warthin<sup>6</sup> was of the opinion that the most important histologic criterion of Basedow's disease, toxic adenoma, and so forth is the presence throughout the thyroid gland of hyperplastic primitive lymph nodes with germinal centers giving evidence of lymphoid exhaustion. Warthin observed that in exophthalmic goiter, toxic adenoma, and so forth the pathologic picture of hyperplasia of the primitive lymph nodes of the thyroid, hyperplasia of the thymus, and other anatomic stigmas of the thymicolymphatic constitution is present. He was of the opinion that Basedow's disease, toxic adenoma, and so forth are pathologic reactions potentially predetermined at birth by virtue of a constitutional anomaly. This constitutional anomaly he preferred to

call "Graves' constitution." He went further and stated that the presence throughout the thyroid gland of hyperplastic primitive lymph nodes with germinal centers which give evidence of lymphoid exhaustion determines the existence of the Graves' constitution and that



Fig. 8.—Multiple, variously sized, well-encapsulated adenomas of the thyroid.

evidence of this constitution may be recognized in the thyroid glands of young children. He considered Graves' constitution to be the underlying pathologic and clinical entity of exophthalmic goiter, toxic goiter, and toxic adenoma.

#### ADENOMATOUS GOITER

Adenomas may occur singly (Fig. 7) but usually they are multiple (Fig. 8). They vary markedly in size, from soft to firm in consistency and from a light amber to a reddish brown in color; they are encapsulated. They may undergo various types of degeneration, such as

hemorrhagic, fibrous, hyaline, calcareous, lipoid (granular), and cystic. Macroscopically and microscopically, true adenomas differ from the surrounding thyroid tissue.

At this point we deem it pertinent to state that we agree with the following statement in the summary of Graham's<sup>7</sup> classical article. He said, "By analogy and by the principles of general pathology, the encapsulated masses of nonlobulated thyroid tissue that do not invade, do not metastasize, and do not present histological characteristics which may be recognized as those of cancer, should be classified among the adenomas until we are sufficiently well acquainted with neoplasms from an etiological and biological standpoint to do otherwise."



Fig. 9.—Adenoma of thyroid (Fig. 7) showing fetal follicles of various sizes and two large follicles containing fairly dense acidophilic colloid (hematoxylin and eosin,  $\times 75$ ).

Microscopically, the arrangement, shape, and size of the follicular cells vary in different adenomas and in different parts of the same adenoma. The cells may appear in diffuse masses without formation of acini (undifferentiated fetal adenoma), in small fetal follicles with small lumina containing no colloid, in large fetal acini with large lumina and with a small content of colloid or in well-differentiated follicles lined by cuboidal or columnar cells, and with large lumina containing

colloid. These adenomas usually contain fetal acini or follicles in addition to well-developed acini which contain colloid (Fig. 9). Columnar epithelium, not infrequently presenting a papillary, infolding effect, appears most often in adenomas associated with the hypertrophic, parenchymatous thyroid gland of exophthalmic goiter, less often in toxic adenoma, a clinical entity recognized and described by H. S. Plummer,<sup>8-10</sup> and rarely in nontoxic adenoma. The toxic adenoma cannot be distinguished macroscopically from the nontoxic adenoma, nor can it always be distinguished microscopically. However, when an adenoma of the thyroid gland is seen in which columnar epithelium is prominent, it is safe to consider it a toxic adenoma; the degree of



Fig. 10—Toxic adenoma on left side showing follicles of various sizes part of which are lined with columnar epithelium with papillary infolding much in evidence. There is a well-defined capsule in the middle with practically normal thyroid gland on the right side (hematoxylin and eosin  $\times 40$ )

toxicity probably depends on the amount of columnar epithelium and on the size and number of such adenomas in the gland. Johnson<sup>11</sup> found intra-adenomatous hypertrophy in 37.4 per cent of cases in which a diagnosis of adenomatous goiter with hyperthyroidism was made, whereas in cases in which the diagnosis was adenomatous goiter without hyperthyroidism he found intra-adenomatous hypertrophy in only 19 per cent. In order to make a microscopic diagnosis of toxic adenoma, the columnar epithelium, which may occasionally be associated with a papillary infolding, must be limited to the adenoma. In other words, the extra-adenomatous thyroid tissue should be practically normal, or at least should not show the microscopic features of exophthalmic goiter (Fig. 10).

## GOITERS INDUCED BY VARIOUS AGENTS

In recent years certain interesting and important forms of goiter have been observed after the administration of a variety of agents. Some of these goiters are now coming to the attention of the pathologist.

One of the first of these forms of goiter to be noted in man was that seen in patients receiving thiocyanates over a prolonged period in the treatment of hypertension. Occasional enlargement of the thyroid gland during the administration of thiocyanates was reported by Barker<sup>12</sup> in 1936, and by Barker, Lindberg, and Wald<sup>13</sup> in 1941. Kobacker<sup>14</sup> in 1942, Fahlund<sup>15</sup> in 1942, and Foulger with Rose<sup>16</sup> in 1943 each reported an instance of enlargement of the thyroid gland following thiocyanate therapy. Rawson, Hertz, and Means,<sup>17, 18</sup> in 1942 and 1943, published a thorough study of thiocyanate goiter in

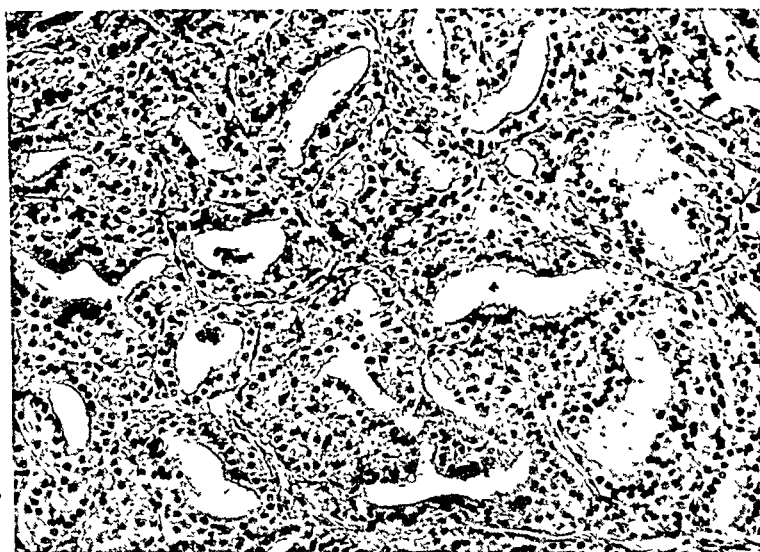


Fig. 11.—Thiocyanate goiter; the pathologic picture is comparable to that of an exophthalmic goiter (hematoxylin and eosin  $\times 125$ ). (Courtesy of Dr. Eugene B. Potter.)

man, with histologic and metabolic studies. Potter<sup>19</sup> in 1944 reported two cases of thiocyanate goiter and described the microscopic findings. In these cases the thyroid gland is enlarged but the metabolic rate is reduced. Exophthalmos is present in some cases. The thyroid gland on biopsy or resection shows parenchymatous hypertrophy (Fig. 11). The gland is cellular; the epithelium is cuboidal to columnar and the colloid generally is scanty or absent. The acini are small. Discontinuance of thiocyanate therapy or administration of desiccated thyroid results in return of the gland to normal size and an elevation of the metabolic rate.

Astwood,<sup>20</sup> and Hertz and Roberts<sup>21</sup> produced similar results in rats, that is, enlargement and hyperplasia of the thyroid gland and lower-



ing of the metabolic rate by the administration of sodium or potassium thiocyanate. Simultaneous administration of potassium iodide inhibited this effect.<sup>20</sup>

Goiter produced by thiocyanates in many respects resembles a form of experimental goiter of great interest since it was first reported by Chesney, Clawson, and Webster<sup>22</sup> in 1928, the so-called "cabbage goiter" or "cyanide goiter." Marked enlargement and hyperplasia of the thyroid gland and a lowering of metabolism developed in rabbits fed on a diet consisting mainly of cabbage. A search for the active agent in cabbage and other Brassica plants demonstrated that cyanides, particularly methyl cyanide, were effective in producing a similar goiter when administered to rabbits.<sup>23</sup> Kennedy and Purves<sup>24</sup> found that they could produce goiter in rats by feeding seeds of the Brassica family (rapeseed).

The cabbage goiters and the cyanide goiters, like those produced by thiocyanate, can be prevented by the simultaneous administration of iodine. The administration of iodine after the development of goiter in rabbits, however, resulted in the onset of symptoms of severe, sometimes fatal, hyperthyroidism.<sup>25</sup>

Other important compounds recently found to have powerful goiter-producing effects fall mainly in two groups: (1) thiourea and various thiourea derivatives and (2) sulfonamides and related substances.

Kennedy<sup>26</sup> in 1942, reasoning that the goiter-producing effect of rapeseed might be due to a derivative of urea, injected allylthiourea into rats and found that it produced large goiters. Richter and Clisby<sup>27</sup> in 1941 produced marked hyperplasia of the thyroid of rats by administration of phenylthiocarbamide. MacKenzie, MacKenzie, and McCollum<sup>28</sup> in 1941 found that the administration of sulfaguani-dine to rats resulted in enlargement of the thyroid, and in 1942 MacKenzie and MacKenzie<sup>29</sup> produced goiters by administering thiourea, diethylthiourea and allylthiourea as well as sulfaguani-dine and other sulfonamide compounds. Astwood, Sullivan, Bissell, and Tyslowitz<sup>30</sup> in 1943 produced enlarged thyroid glands in rats with both sulfonamide compounds and thiourea.

The thyroid glands in the animals treated with thiourea and thiourea compounds are diffusely enlarged and reddened, and the vessels are enlarged. Microscopically the height of the acinar cells and loss of colloid from the follicles are increased greatly in this type of goiter. The follicles are increased in size and appear to be increased in number. The lumina are decreased in size, due in part to many papillary projections; some follicles are solid round or oval masses of cells.<sup>30</sup>

Astwood<sup>20</sup> in 1943 tested various compounds and found that 39 out of 106 substances used were effective in causing enlargement and hyperplasia of the thyroid gland in rats. He found that thiouracil, a derivative of thiourea, was the most effective substance in the thiourea group. Of the sulfonamide drugs and other derivatives of aniline,

sulfadiazine had the most active effect on the thyroid gland. Feldman, Hinshaw, and Mann<sup>71</sup> in 1944 in administering to guinea pigs a sulfone derivative, promizole, found that the thyroid glands became enlarged and hyperplastic. Higgins and Larson<sup>72</sup> in 1944 confirmed this result in rats.

It is of interest that the experimental production of goiter by cyanides and thiocyanates has been prevented by the simultaneous administration of iodine, whereas the goitrogenic effect of thiourea and sulfanilamide and related compounds cannot be prevented by administration of iodine, but can be prevented by the administration of desiccated thyroid or thyroxin. Administration of desiccated thyroid or thyroxin was also effective in reducing goiters after they had developed regardless of whether they had followed administration of cyanides, thiocyanates, thiourea, or sulfonamide compounds.

It has been assumed that the action of the various drugs which produce goiter is by means of an inhibition of, or interference with, the manufacture of the normal thyroid hormone.<sup>18, 33</sup> The resulting increase in activity of the thyroid-stimulating pituitary hormone brings about hyperplasia of the thyroid cells but does not bring about an increase in thyroid hormone, which is in fact reduced to subnormal levels. This inhibitory effect has been made use of clinically by the administration of thiourea or thiouracil to patients suffering from hyperthyroidism in the form of Graves' disease.<sup>34-36</sup> In addition to disappearance of toxic symptoms and a decrease in the basal metabolic rate, temporary increase in the size of the thyroid gland was observed in three of nine patients treated with thiouracil by Williams and Bissell.<sup>36</sup> Microscopically the thyroid gland in cases of Graves' disease treated with thiouracil shows extreme hyperplasia with heightened epithelium, marked papillary infolding, and mitosis in the epithelial cells.

We should like to take this opportunity to record our impression that in the thiocyanate goiter there is more cellular hypertrophy, it is therefore more nearly comparable microscopically to an exophthalmic goiter, and that the thiouracil goiter is more of a cellular hyperplasia with mitosis very much in evidence, and is therefore more comparable to a carcinoma of the thyroid.

#### REFERENCES

1. Haines, S. F.: Personal communication to the authors.
2. Hertzler, A. E.: *Diseases of the Thyroid Gland Presenting the Experience of More Than Forty Years*, New York, 1941, Paul B. Hoeber, Inc., pp. 74-76.
3. Plummer, H. S.: Discussion, *Tr. A. Am. Physicians* 39: 178-179, 1924.
4. MacCarty, W. C.: *Pathological Anatomy of Goiter*, New York State J. Med. 12: 595-599, 1912.
5. MacCarty, W. C.: *Goiter and Its Relation to Its Structural and Physiological Units*, Surg., Gynec. & Obst. 16: 406-411, 1913.
6. Warthin, A. S.: Constitutional Entity of Exophthalmic Goiter and So-Called Toxic Adenoma, *Ann. Int. Med.* 2: 553-570, 1928.
7. Graham, Allen: Nodular Goiters: Their Relation to Neoplasia, *Am. J. Surg.* 7: 163-173, 1929.

8. Plummer, H. S.: The Clinical and Pathological Relationship of Simple and Exophthalmic Goiter, *Am. J. M. Sc.* 146: 790-795, 1913.
9. Plummer, H. S.: The Clinical and Pathologic Relationships of Hyperplastic and Nonhyperplastic Goiter, *J. A. M. A.* 61: 650-651, 1913.
10. Plummer, H. S.: Discussion, *Tr. A. Am. Physicians* 39: 178-179, 1924.
11. Johnson, J. R.: A Study of Nodular and Adenomatous Goiters With and Without Hyperthyroidism, Thesis, Graduate School of the University of Minnesota, 1943, 57 pp.
12. Barker, M. H.: The Blood Cyanates in the Treatment of Hypertension, *J. A. M. A.* 106: 762-767, 1936.
13. Barker, M. H., Lindberg, H. A., and Wald, M. H.: Further Experiences With Thiocyanates; Clinical and Experimental Observations, *J. A. M. A.* 117: 1591-1594, 1941.
14. Kobacker, J. L.: Production of Goitre and Myxedema by Sulfoeyanates, *Ohio State M. J.* 38: 541-542, 1942.
15. Fahlund, G. T. R.: Painful Enlargement of the Thyroid Gland, a Manifestation of Sensitivity to Thiocyanate, *Proc. Staff Meet., Mayo Clin.* 17: 289-293, 1942.
16. Foulger, Margaret P. H., and Rose, Edward: Acute Goiter During Thiocyanate Therapy for Hypertension, *J. A. M. A.* 122: 1072-1073, 1943.
17. Rawson, R. W., Hertz, Saul, and Means, J. H.: Cyanate Goiter in Man, Report of a Case With Histological and Metabolic Studies, *J. Clin. Investigation* 21: 624, 1942.
18. Rawson, R. W., Hertz, S., and Means, J. H.: Thiocyanate Goiter in Man, *Ann. Int. Med.* 19: 829-842, 1943.
19. Potter, E. B.: Acute Goiter Due to Cyanate Therapy; Report of Two Cases With Thyroidectomy, *J. A. M. A.* 124: 568-570, 1944.
20. Astwood, E. B.: The Chemical Nature of Compounds Which Inhibit the Function of the Thyroid Gland, *J. Pharmacol. & Exper. Therap.* 78: 79-89, 1943.
21. Hertz, S., and Roberts, A.: Quoted by Rawson, R. W., Hertz, S., and Means, J. H.<sup>18</sup>
22. Chesney, A. M., Clawson, T. A., and Webster, Bruce: Endemic Goitre in Rabbits. I. Incidence and Characteristics, *Bull. Johns Hopkins Hosp.* 43: 261-277, 1928.
23. Marine, David, Spence, A. W., and Cipra, Anna: Production of Goiter and Exophthalmos in Rabbits by Administration of Cyanide, *Proc. Soc. Exper. Biol. & Med.* 29: 822-823, 1932.
24. Kennedy, T. H., and Purves, H. D.: Studies on Experimental Goitre; Effect of Brassica Seed Diets on Rats, *Brit. J. Exper. Path.* 22: 241-244, 1941.
25. Webster, Bruce, and Chesney, A. M.: Endemic Goitre in Rabbits. III. Effect of Administration of Iodine, *Bull. Johns Hopkins Hosp.* 43: 291-308, 1928.
26. Kennedy, T. H.: Thio-ureas as Goitrogenic Substances, *Nature, London* 150: 233-234, 1942.
27. Richter, C. P., and Clisby, K. H.: Graying of Hair Produced by Ingestion of Phenylthiocarbamide, *Proc. Soc. Exper. Biol. & Med.* 48: 684-687, 1941.
28. MacKenzie, Julia B., MacKenzie, C. G., and McCollum, E. V.: The Effect of Sulfanilylguanidine on the Thyroid of the Rat, *Science* 94: 518-519, 1941.
29. MacKenzie, Julia B., and MacKenzie, C. G.: The Effect of "Sulfa" Drugs on the Thyroid Gland in Rats and Mice, *Federation Proc.* 1: 122-123, 1942.
30. Astwood, E. B., Sullivan, J., Bissell, Adele, and Tyslowitz, R.: Action of Certain Sulfonamides and of Thiourea Upon the Function of the Thyroid Gland of the Rat, *Endocrinology* 32: 210-225, 1943.
31. Feldman, W. H., Hinshaw, H. C., and Mann, F. C.: The Effect on Previously Established Tuberculosis in Guinea-Pigs of 4,2'-diaminophenyl-5'-thiazolyl-sulfone (Promizole), *Am. Rev. Tuberc.* (In press.)
32. Higgins, G. M., and Larson, R. A.: Hyperplasia of the Thyroid Gland Induced by 4,2'-diaminophenyl-5'-thiazolesulfone (Promizole), *Proc. Staff Meet., Mayo Clin.* 19: 137-141, 1944.
33. Franklin, A. L., and Chaikoff, I. L.: The Effect of Sulfanilamide on the Conversion in Vitro of Inorganic Iodine to Thyroxine and Diiodotyrosine by Thyroid Slices, *J. Biol. Chem.* 148: 719-720, 1943.
34. Astwood, E. B.: Treatment of Hyperthyroidism With Thiourea and Thiouracil, *J. A. M. A.* 122: 78-81, 1943.
35. Himsworth, H. P.: Thyrotoxicosis Treated With Thiourea, *Lancet* 2: 465-466, 1943.
36. Williams, R. H., and Bissell, G. W.: Thiouracil in Treatment of Thyrotoxicosis, *New England J. Med.* 229: 97-108, 1943.

# DIAGNOSIS OF THYROTOXICOSIS

WILLARD O. THOMPSON, M.D., CHICAGO, ILL.

(From the Department of Medicine, University of Illinois College of Medicine  
and the Presbyterian Hospital)

## DEFINITION

THE term thyrotoxicosis applies to exophthalmic goiter, toxic adenoma, and mixed types of toxic goiter. Many investigators have come to the conclusion that the underlying pathology of exophthalmic goiter and toxic adenoma is the same and that any differences that are noted in the clinical picture are the result of variations in the response of the individual patient to the thyroid intoxication. This point of view is still not completely established. However, for the purpose of this article, all types of toxic goiter may be grouped together under the general term thyrotoxicosis.

## SIGNS AND SYMPTOMS OF THYROTOXICOSIS

The most outstanding manifestations of thyrotoxicosis are:

Goiter

Nervousness and irritability

Tremor

Tachycardia

Palpitation

Other signs and symptoms of the disease are:

Exophthalmos

Loss of weight in spite of a good appetite

Increase in basal metabolism

Dyspnea and, in a few patients, cardiac decompensation

Increased perspiration, flushing of the skin, and dermatographia

Systolic thrill and bruit over the thyroid

Emotional instability

Muscle weakness

Ease of fatigue

Fever

Nausea and vomiting

Diarrhea

Pressure symptoms from the goiter

Scantiness of menstruation and, in a few patients, rather long periods of amenorrhea

Increased excretion of calcium and decalcification of bone

*Goiter.*—Some differences between the syndrome known as exophthalmic goiter and that known as toxic adenoma should be pointed out.

Received for publication, July 10, 1944.

In general, the onset of the disease is much more abrupt in patients with exophthalmic goiter. Plummer estimated that in the patients seen at the Mayo Clinic, fourteen and one-half years elapsed, on the average, from the time of appearance of a nodular goiter until the onset of hyperthyroidism. The term exophthalmic goiter is a misnomer because the disease may be present without exophthalmos and without a goiter, although it is most unusual to observe the absence of both in the same patient. Even though the thyroid gland may not be enlarged, it is usually much firmer than normal and in patients who show very little enlargement, the increased firmness may be an important diagnostic sign, particularly if it is associated with the presence of a systolic bruit over one or both of the superior poles. A bruit and thrill do not occur in the normal gland. The problem of diagnosis is sometimes complicated by the fact that a large portion of the thyroid or even all of it may be in the substernal area. As a rule, only a portion of the gland lies substernally and when most of it is in the substernal space the upper edge can be palpated, particularly when the patient swallows. The presence of substernal nodules can often be detected by careful palpation during the act of swallowing. When thyroid tissue cannot be palpated, it can sometimes be demonstrated by roentgen-ray examination of the chest. The rare finding of the thyroid tissue below the level of the mediastinum, for example just above the diaphragm, may be borne in mind in some unusual cases in which thyrotoxicosis appears to be present but thyroid tissue cannot be located. It may be emphasized that it is unusual to be unable to palpate any thyroid tissue in patients with thyrotoxicosis, and goiters that are entirely confined to the substernal space so that no portion of them can be palpated are rare.

It is very important to use the correct method of palpating the thyroid. Best results are obtained by standing behind rather than in front of the patient. It is preferable to have the patient in the sitting position. The head may, if desired, be rotated slightly toward the side to be examined in order to relax the sternomastoid muscle. The trachea is displaced to one side by pressing against it with the fingers of one hand. The thyroid tissue on the opposite side of the neck may then be palpated by placing the thumb behind the sternomastoid and the fingers in front, taking care not to confuse muscle tissue with thyroid tissue. By manipulating both hands at the same time and having the patient swallow, it is possible to palpate almost all thyroid tissue that is present in the neck and also to feel the lower extremity of most goiters which have some substernal extension and to feel the upper end of most truly substernal goiters. Tissue on the opposite side of the neck is palpated by reversing the position of the hands and, if desired, rotating the head slightly toward that side. It is possible with careful palpation to outline all normal thyroid glands. Those that cannot be

palpated are usually very small and atrophic. Palpation is of great importance in doubtful cases. The detection of abnormal thyroid tissue, for example the presence of a few small nodules which extend sub-sternally, may be the determining factor in deciding whether or not the patient has thyrotoxicosis.

In symmetrical enlargements of the gland with hyperthyroidism, a bruit which is systolic in time is frequently heard. It is usually most marked over the superior poles and may be audible all over the gland. It may or may not be accompanied by a systolic thrill. In nodular goiters with hyperthyroidism, a thrill and bruit are usually not heard.

Pressure symptoms from the goiter are noted in about one-third of the patients. They are usually not serious unless the goiter extends into the substernal space. Some distortion and compression of the trachea may occur. The pressure symptoms of toxic goiter must not be confused with the sensation of a lump in the throat which is so common in nervous women who do not have thyrotoxicosis.

*Nervous Manifestations.*—The nervousness of toxic goiter is fairly typical. It is characterized by restlessness, inability to sit still, irritability, and sudden fits of weeping without much justification. Many patients are easily frightened, worry a great deal, and are very sensitive before the onset of the disease. These tendencies are exaggerated after the development of toxic goiter. It is not always easy to be certain when nervousness and emotional instability are caused by thyrotoxicosis and when they are the result of some domestic difficulty or one of the other major problems of living. The nervous manifestations may be similar in both instances. In the case of toxic goiter, it is the combination of nervousness, irritability, and emotional instability with other manifestations of the disease which makes the diagnosis possible. A large percentage of patients referred to a thyroid clinic with the tentative diagnosis of thyrotoxicosis prove to have no overactivity of the thyroid at all and often are nervous women with domestic problems.

In general, the nervous manifestations of the disease are greater in patients with exophthalmic goiter than in those with toxic adenoma. Indeed, the presence or absence of emotional instability was considered by Plummer to be the most important sign in distinguishing between these two diseases.

*Tremor.*—The tremor of thyrotoxicosis is fine and rapid in contrast to the coarser, slower tremor of Parkinson's disease. There are, however, exceptions to every rule and in some instances the tremor is coarse. It should be pointed out that Parkinson's disease is sometimes accompanied by a syndrome resembling exophthalmic goiter. This phenomenon is of interest in view of the reported production of thyrotoxicosis in animals by injury to the base of the brain.

*Cardiac Manifestations.*—Palpitation and tachycardia are the rule. The most common finding is rapid, forceful beating of the heart. The

heart beats are often so forceful that they shake the whole chest wall. In a few instances the heart rate may be very little increased in spite of a great increase in the basal metabolism. In rare instances in which complete heart block is present, the onset of thyrotoxicosis may cause the heart rate to rise approximately to the normal level. A rough parallelism has been noted between the product of the pulse rate and pulse pressure and the level of the basal metabolism.

Dyspnea is common, particularly on effort. The increased work demanded of the heart is sometimes enough to produce cardiac decompensation, especially when the heart is independently damaged. Both transient and prolonged attacks of auricular fibrillation are not uncommon. Auricular flutter is rare. The onset of auricular fibrillation or cardiac decompensation or both usually means that the heart is independently damaged by arteriosclerosis or rheumatic fever. Attacks of true angina pectoris are not very common and when they do occur, tend to disappear after the disease has been abolished by suitable treatment. The presence of thyrotoxicosis must always be thought of in patients with unexplained auricular fibrillation and cardiac decompensation. The diagnosis is not always easy, particularly when toxic goiter occurs in apathetic individuals. The nervous manifestations of the disease may then be almost absent and what few there are can be elicited only by the most careful examination of the patient. Cardiac decompensation in itself may produce a considerable amount of increase in the basal metabolism.

The dyspnea of thyrotoxicosis is probably due in part to a specific chemical effect of the thyroid hormone on the heart muscle, as well as to overwork of the heart. The ease with which skeletal muscle fatigues in this disease is probably the result of a similar disturbance. Mechanical factors alone explain only part of the picture.

Neurocirculatory asthenia is sometimes confused with thyrotoxicosis because of nervousness, ease of fatigue, rapid forceful beating of the heart, and some increase in pulse pressure. Exophthalmos is not present. There is usually no goiter and the basal metabolism is normal.

*Exophthalmos.*—Exophthalmos of varying degree is noted in from 60 to 70 per cent of patients with exophthalmic goiter but is not commonly noted in persons with nodular goiters and hyperthyroidism. In determining the degree of exophthalmos, it is important to bear in mind the natural prominence of the patient's eyes before the onset of the disease. Puffiness of the eyelids is a very characteristic finding and is sometimes of more diagnostic value than exophthalmos. The prominence of the eyes may vary greatly in the same patient from time to time and varies greatly from patient to patient. One eye is often more prominent than the other. A great variety of eye signs have been described but only two of them are of much practical importance, namely, lid lag (von Gräfe) and poor convergence (Moebius). As the

exophthalmos increases, the movements of various extraocular muscles may be impaired, producing many abnormalities in the movements of the eyeball. When the condition is so marked that the eyelids cannot be closed, there is great danger of the development of a corneal ulcer. The condition may be so extreme that a prolapse of the eyeball occurs and it is occasionally necessary to resort to operative procedures in order to correct these malignant forms of exophthalmos. Exophthalmos may be the first sign of exophthalmic goiter and may precede the onset of an increase in basal metabolism by as much as six months. Bilateral exophthalmos means exophthalmic goiter until proved otherwise. When the condition is strictly unilateral it is necessary to consider the possibility of a tumor of the orbit pushing the eyeball forward.

*Loss of Weight.*—One of the most characteristic features of toxic goiter is loss of weight in spite of an increase in appetite. This phenomenon is the result of the increase in basal metabolism. Loss of weight is not invariable and weight may be gained if the ingestion of calories is sufficient to exceed the expenditure. The loss of weight may be rapid and extreme and, in general, the greater the loss of weight the more serious the condition of the patient. In gauging the risk of operation more attention is paid to the general nutritional state of the body than to any other factor. The most common conditions in which similar extreme loss of weight may be encountered are diabetes mellitus, pulmonary tuberculosis and other chronic infections, and carcinoma. The excretion of nitrogen in the urine of patients with toxic goiter may be very high, indicating rapid breakdown of tissue. For this reason, it is very important that the diet be high not only in calories but also in protein.

In diabetes mellitus weight is sometimes lost in spite of a good appetite. The presence of large amounts of sugar in the urine leaves little doubt about the diagnosis. However, toxic goiter and diabetes mellitus sometimes occur together. The diagnosis is then made by the finding of a high basal metabolism, goiter, nervousness, increased perspiration, and all the other manifestations of toxic goiter, together with the presence of large quantities of sugar in the urine and other manifestations of diabetes mellitus. While traces of sugar may be found in the urine of patients with toxic goiter without diabetes, the presence of large quantities almost invariably means that the patient has diabetes mellitus. When the glycosuria is mild and requires only small amounts of insulin for its control, it may disappear after a thyroidectomy.

Although pulmonary tuberculosis is commonly stated to be confused with toxic goiter, in our experience it rarely presents any problem. Pulmonary tuberculosis does result in loss of weight, tachycardia, and ease of fatigue, but is readily distinguished from toxic goiter by the poor appetite, normal basal metabolism (unless a fever is present),



absence of goiter, characteristic roentgen-ray findings, and the recovery of tubercle bacilli in the sputum and fasting gastric contents.

*Gastrointestinal Symptoms.*—Diarrhea occurs in less than one-third of the cases and usually in the more severe ones. An increase in appetite is the rule but in a few patients nausea and vomiting are noted. When present, they indicate that the disease is very severe and are strong presumptive evidence of an impending crisis. They are to be regarded in the most serious light and mean that treatment must be started at once. They sometimes persist in spite of the administration of iodine and under these circumstances indicate a bad prognosis.

*Muscle Weakness.*—Muscle weakness is almost always present to some extent and is easily demonstrated by difficulty in stepping up on a chair. The intensity of muscle weakness and emotional instability are directly related to the severity of the disease and the risk involved in operation. The development of muscle weakness is undoubtedly the result of a chemical disturbance in the muscle and is probably related to the metabolism of phosphocreatine. Muscle weakness diminishes as weight is gained during the administration of a high caloric diet which is high in protein.

*Ease of Fatigue.*—Ease of fatigue goes hand in hand with muscle weakness and bears a direct relationship to the severity of the disease. However, exceptions are noted and in some patients the disease produces at first an exhilaration and apparently increases the capacity for work.

*Cutaneous Manifestations.*—The skin is commonly warm, moist and flushed, although pallor may be present and there may be little increase in perspiration. The skin flushes easily just as it does in women with the menopausal syndrome and there is usually a dermatographia.

*Fever.*—The temperature of the body is usually normal but in occasional instances a moderate elevation of the temperature appears to be explained only by the presence of thyrotoxicosis.

*Menstrual Disturbances.*—Scantiness of menstruation is common in toxic goiter just as profuse bleeding is common in hypothyroidism. The intermenstrual periods may be greatly prolonged. The longest period of amenorrhea which we have observed is nine months.

*Effect on Calcium Metabolism.*—Hyperthyroidism results in an increased excretion of calcium in the urine without any change in the concentration of calcium in the serum, in contrast to hyperparathyroidism which causes an increase both in the excretion of calcium in the urine and in the concentration of calcium in the serum. When hyperthyroidism is present for a long period of time, extensive decalcification of bone may result if the intake of calcium is low. Spontaneous fractures have been reported in rare instances as a result of this change. A minister is reported suddenly to have grown two or three inches shorter one Sunday while preaching, a few weeks after a thyroidectomy. He had suffered from spontaneous fractures of two vertebrae. On

roentgenologic examination the only change noted in hyperthyroidism is uniform decalcification. The bone cysts characteristic of hyperparathyroidism are not observed.

*Increase in Basal Metabolism.*—The most important laboratory guide to fluctuations in thyroid function is the determination of the basal metabolism. However, it is not to be relied upon too greatly and is not a substitute for a careful history and physical examination. It is, however, a very important aid in diagnosis and in following the effect of treatment. Too much emphasis cannot be placed upon the value of determining the level of basal metabolism instead of relying upon a single test. Before carrying out any treatment, the metabolism should be determined on successive days until a level is reached. Only in this way is it possible to determine the severity of the disease as judged by the amount of increase in basal metabolism and also to measure the effect of treatment, in particular that of iodine. In hospital patients the first metabolism is, on the average, about fifteen points higher than the level which is subsequently established. If a single determination is relied upon, false conclusions may be drawn. If the elevation is only moderate, the metabolism may drop to normal when it is repeated. False diagnoses of thyrotoxicosis may thereby be avoided. The amount of elevation of the basal metabolism bears a rough relationship to the severity of the disease, although many exceptions are noted. In general, the rate must be consistently elevated 15 per cent or more above the normal before it can be concluded that thyrotoxicosis is present. In doubtful cases, the influence of iodine or thiouracil on the rate of metabolism may be of diagnostic value. If the metabolism is reduced and the symptoms are alleviated during the administration of iodine or thiouracil, and the two increase when the administration of these drugs is discontinued, it may be assumed that thyrotoxicosis is present. The response to iodine is of special value when the increase in metabolism is slight and yet the symptoms of the disease appear to be definite. Under these circumstances, the administration of iodine may reduce the metabolism to a normal or even to a subnormal level. In rare instances, particularly following a subtotal thyroidectomy, patients appear to be thyrotoxic in spite of the presence of a normal level of metabolism. In such patients the rate may drop to between minus 15 and minus 25 per cent in association with clinical improvement. Nervousness will reappear when iodine is omitted and the metabolism rises to normal. In such patients the subnormal level of metabolism produced by iodine may possibly represent their true normal level, so that a standard normal level would be, for them, a thyrotoxic one. In other patients with a normal level of metabolism following operation, the administration of iodine may produce myxedema with a lowering of the metabolism. These abnormalities disappear when the administration of iodine is discontinued.

Observation of the influence of thiouracil on the basal metabolism may now be substituted for that of iodine in many patients as a diagnostic procedure. The chief objection to thiouracil for this purpose is that a much longer period of time is required for the maximum effect on the metabolism to appear (from thirty to thirty-five days, compared with from seven to ten days for iodine).

#### OTHER DISEASES IN WHICH THE BASAL METABOLISM IS ELEVATED

Thyrotoxicosis is not the only cause of an increase in basal metabolism. It may be elevated in the following conditions:

1. Acromegaly
2. Lymphatic and myelogenous leucemia.
3. Essential hypertension
4. Overdose of desiccated thyroid or thyroxine
5. Administration of various drugs such as dinitrophenol, dinitro-ortho-cresol, diiodothyronine, adrenalin, caffeine, atropine, camphor
6. Exercise
7. Ingestion of food
8. Fever
9. Pregnancy
10. Cardiac decompensation
11. Polycythemia vera
12. Pernicious anemia

*Acromegaly.*—In some patients with acromegaly a syndrome resembling exophthalmic goiter may be present with moderate exophthalmos, goiter, palpitation, tremor, increased perspiration, and a high basal metabolic rate. These symptoms are the result of overproduction of the thyrotropic factor by the anterior lobe of the pituitary. Indeed, overproduction of this factor may be an important cause of thyrotoxicosis. When acromegaly is well developed, the diagnosis is easy. In the early stages of the disease before the skeletal changes have become clear-cut, it may be difficult to determine whether acromegaly is present or not. Accurate diagnosis is important because when thyrotoxicosis is associated with acromegaly, it is treated by attacking the pituitary and not the thyroid. It should be emphasized that in the thyrotoxicosis accompanying acromegaly, a reduction in basal metabolism is noted during the administration of iodine, just as it is in thyrotoxicosis without acromegaly.

*The Leucemias.*—Increases in basal metabolism of as much as 70 per cent may be noted in patients with lymphatic and myelogenous leucemia. The increase appears to be somewhat proportional to the increase in the white cell count and is reported to drop when the disease improves with roentgen-ray therapy. The clinical pictures in the leucemias are so different from those presented by thyrotoxicosis that they

rarely give rise to problems in diagnosis, although exophthalmos, high pulse rate, and increased sweating may be present. There are reports of confusion in the literature.

*Essential Hypertension.*—In a fairly large percentage of patients with essential hypertension there is an increase in basal metabolism of as much as 30 per cent. Its cause is obscure. When associated with a goiter, it sometimes results in an incorrect diagnosis of thyrotoxicosis and leads to a thyroidectomy. It does not disappear, however, following this operation. Observation of the influence of iodine and thiouracil on the basal metabolism in these patients is of great diagnostic value.

*Overdose of Desiccated Thyroid or of Thyroxine.*—In a few obese patients a syndrome resembling thyrotoxicosis is observed following the ingestion of excessive amounts of desiccated thyroid or of thyroxine for purposes of weight reduction. Elevations in basal metabolism of as much as 50 per cent are sometimes observed. If the patient happens to have a goiter, the presence of loss of weight, tremor, increased perspiration, and palpitation may make the diagnosis difficult. In doubtful cases it is always wise to inquire about the ingestion of thyroid products. Symptoms disappear promptly following the omission of the drug.

*Administration of Various Drugs.*—Increases in basal metabolism from the administration of various drugs do not present very much of a diagnostic problem. Great increases in metabolism may be produced by dinitrophenol and dinitro-ortho-cresol, which appear and disappear much more quickly following the administration and omission of these drugs than after the administration and omission of the thyroid hormone. The clinical picture produced by these two drugs is quite different from that produced by thyrotoxicosis. For example, patients with myxedema remain myxedematous when the basal metabolism is raised from minus 40 per cent to normal by their administration. Diiodothyronine (thyroxine minus 2 atoms of iodine) produces an increase in basal metabolism which also appears and disappears more quickly following the administration of the drug, than does that produced by the thyroid hormone. This material is used only experimentally and therefore does not present a problem in diagnosis. Adrenalin produces a moderate increase in basal metabolism which reaches its maximum in fifteen minutes and disappears in sixty minutes after administration of a single dose. Following a single dose of 10 mg. of thyroxine intravenously to an individual with a normal level of metabolism, the maximum increase appears within two to three days and disappears within twenty days. In patients with myxedema, the maximum appears within three to ten days and disappears within seventy to ninety days. Overproduction of adrenalin may present a diagnostic problem in rare instances in which there is a tumor of the adrenal medulla. Other manifestations of the disease are different from those of thyrotoxicosis and tend to occur in paroxysms. Caffeine is reported

to cause an increase in basal metabolism of from 7 to 23 per cent in a dose of from 0.5 to 0.7 Gm. and atropine and camphor are reported to produce somewhat smaller increases. The minor effects of these drugs merely emphasize the necessity of carrying out basal metabolism determinations under basal conditions.

*Exercise.*—There is a direct relationship between heat production in muscular exercise and the amount of energy expended in the muscular activity. There is a direct parallelism between the minute volume of the heart and the increase in basal metabolism.

*Ingestion of Food.*—Slight increases in basal metabolism have been observed following the ingestion of various foodstuffs, particularly protein, which exerts a specific dynamic action greater than that of carbohydrate or fat. Following the ingestion of very large quantities of protein and basal metabolism may rise as much as 20 per cent.

*Fever.*—An increase in basal metabolism has been noted in patients with fever, which amounts approximately to 7 points for each degree Fahrenheit that the temperature is raised and 10 points for each degree centigrade.

*Pregnancy.*—Increases in basal metabolism of as much as 25 per cent may be noted in the last three months of pregnancy. The increase has been commonly considered to be proportional to the combined surface area of the mother and child, although some of the increases are greater than could be accounted for in this manner. In rare instances, increases of as much as 40 per cent have been noted and seem to be explained only by some hormonal change involving increased production of thyroxine, which in turn may be secondary to some pituitary disturbance. In patients with goiters, either before or after thyroidectomy, it is not always easy to be certain when an increase in basal metabolism is entirely the result of the pregnancy and when it is the result of some overactivity of the thyroid. A diagnostic trial of iodine administration may be helpful.

*Cardiac Decompensation.*—In patients with cardiac decompensation the basal metabolism may rise as much as 50 per cent above normal. This increase rarely presents a diagnostic problem because it is unusual to carry out basal metabolism determinations in patients with cardiac decompensation.

*Polycythemia Vera and Pernicious Anemia.*—In polycythemia vera and pernicious anemia slight increases in basal metabolism have been reported but these diseases do not present diagnostic problems.

# THE HEART AND CIRCULATION IN PATIENTS WITH HYPERTHYROIDISM

ROBERT W. KEETON, M.D., CHICAGO, ILL.

(From Department of Medicine, University of Illinois, College of Medicine, and  
Illinois Research and Educational Hospitals)

THE problems encountered in the treatment of the heart in patients with hyperthyroidism can best be understood by a study of the effects of hyperthyroidism on the physiologic behavior of the normal circulation. It is clear that if the patient has already acquired heart disease prior to the hyperthyroidism the pathologic changes will be influenced by both processes. In general the changes in the physiology of the circulation can be attributed largely to overwork and under-nutrition. This discussion will be guided by this concept.

## RESPONSE OF THE CIRCULATION TO THE PRODUCTION OF EXTRA HEAT

*Peripheral Blood Flow.*—The patient with hyperthyroidism has an increased energy expenditure and a corresponding heat production. The heat is liberated within the body, largely in the muscles, and is transported to the surface by the blood. The surface is a complex structure composed of three units which are functionally integrated to regulate the loss of heat. The outer or papillary layer has immediately beneath it, capillaries through which the blood flows from the arterioles, and it is exposed to the temperature of the surrounding environment. Beneath this is a subpapillary layer of capillary and venous plexuses. According to Wollheim<sup>1</sup> this layer acts as a reservoir in which the blood becomes trapped and through which the blood moves from five to twenty-five times slower than in the adjacent end capillaries of the skin papillae. Attention has been drawn previously to this depot function of the skin by Meek and Eyster.<sup>2</sup> The blood thus withdrawn from the circulation may at times amount to 1,800 c.c. Finally there is the subcutaneous layer, which contains variable amounts of fat and a plexus of larger vessels. The quantity of fat and fluid present in this layer modifies its character and changes its capacity for the transfer of heat.<sup>3</sup>

As the blood circulates through this surface layer its temperature is reduced and approximates that of the surface of the skin. The rectal temperature measures the temperature of the blood at the sites of heat formation and at its entrance to the surface. The difference between the skin and rectal temperatures gives the gradient of heat flow. If the rectal temperature does not change, then all the heat produced is being eliminated. Knowing the amount of heat produced in a unit's time (basal metabolic rate), the specific heat of the blood,

and the difference between the skin and rectal temperatures, the quantity of blood required to deliver this amount of heat to the surface can be computed. This quantity of blood represents the peripheral blood flow. If the peripheral layer is exposed to a cool environment, loss of heat by radiation occurs readily, the skin temperature is decreased, the gradient of heat flow is increased, and a smaller blood flow will be required. If the environment is warm but relatively dry, then the insensible perspiration is easily vaporized, the surface is cooled, the gradient is maintained, and the blood flow is reduced. Under hot moist environments (tropical conditions), the surface cannot be cooled, the gradient will be reduced, and the blood flow will be increased to a maximum. Unless the heat produced in a unit's time can be transported to the surface and eliminated in the same unit of time, it will be stored in the body and its storage will be reflected in the rise of the rectal temperature. Increase in rectal temperature is associated with an increase in heat production of 7 per cent for every degree rise (F.) in temperature. Thus storage of heat leads to the development of a vicious cycle. Keeton and co-workers<sup>4</sup> using this method have reported that normal subjects exposed to hot moist environments may increase their peripheral blood flow as much as seven times as compared to the blood flow under comfortable conditions. Under such an increased blood flow there was no storage of heat and no increase in heat production. Stewart and Evans<sup>5</sup> using similar methods have studied the peripheral blood flow in patients with hyperthyroidism who were exposed to an average environmental temperature. They found that the peripheral blood flow bears a linear relationship to the basal metabolic rate, and concluded that this increase in blood flow was correlated with heat disposal. The clinical signs of maximal vasodilatation seen in hyperthyroid states are familiar to all. They consist of the warm, moist, flushed skin, capillary pulsation, and low diastolic blood pressure.

*Increase in Blood Volume.*—If the blood flow through the periphery is increased from three to seven times it is obvious that the extra blood must be obtained by either shunting it from the interior (viscera, lungs, muscles) to the surface or by increasing the circulating volume. Keeton and associates<sup>6</sup> have shown in conditions where there is an embarrassment in heat elimination unassociated with an increase in heat production the circulating blood volume is not regularly increased. The blood is obtained by shunting it from the interior. The extra blood is obtained from the reserve depots, the subpapillary layer of skin, spleen, liver, and lungs. The conversion of a slowly moving stream of blood normally present in the subpapillary layer to a rapidly moving one, and the establishment of a free access of the circulating blood volume to this peripheral layer serves the double purpose of giving a larger volume of blood for the convection of the heat and a more advantageous disposition of the blood for heat loss.

In hyperthyroidism with its extra heat production, the peripheral blood flow is maintained not only by shunting blood from the interior but also by an actual increase in blood volume.<sup>7</sup>

*Acceleration of Blood Flow.*—In the normal subject at work, extra heat is produced. The heart responds by increasing its rate and its output per minute. This adjustment may be explained, in part, as secondary to the increased filling of the heart and the increased circulating volume. In hyperthyroidism the increase in cardiac output is greater at the same oxygen consumption than it is in work. This suggests that the heart in hyperthyroidism is hyper-reactive and that there are other factors than the demand for the transport of extra heat operative. This view is supported by the report of various investigators<sup>8</sup> who found that if a rabbit is rendered hyperthyroid by thyroid feeding and the heart is then removed, the isolated organ continues to beat at a rate much faster than the heart of a normal control. This view is further supported by the clinical observation that in patients with good compensation tachycardias exist which are out of proportion to the increases in their basal metabolic rates. This acceleration of the circulation can be approximately measured by determining the circulation time (arm to tongue). Clinically this activity of the circulation is revealed by a diffuse precordial pulsation, widespread pulsations of the arteries, loud abrupt apical heart tones, and increased pulse pressure.

#### BEHAVIOR OF THE CIRCULATION IN VASOMOTOR INSTABILITY WITH NORMAL HEAT PRODUCTION

The circulatory adjustments of patients with vasomotor instability must be understood if errors in diagnosis are to be avoided. These patients present bizarre clinical pictures, and are classified variously by the examining physicians. One man will say that the patient is suffering from somatic fixation, another will find that he has a cardiac neurosis or anxiety state, but all will wonder whether the patient may not have hyperthyroidism. It is quite helpful to think of these individuals as suffering from vasomotor instability and to assume that there may be many causes for this instability. The differential diagnosis hinges on the fact that although they may appear to be producing extra heat, in reality they have a normal heat production. If one looks for signs of increased peripheral blood flow, they will be lacking. The skin may be flushed over the face and neck, but it will not be rosy elsewhere. If the hand is held over the skin a sensation of warmth will not be felt as in hyperthyroid patients. The skin may be moist in places but it feels cold. Goldbloom<sup>9</sup> has shown that in these patients neither the blood volume nor the cardiac output is increased. The physiologic difficulty lies in the adjustment of heart action to the changing vascular bed produced by reflex stimulation of various types. The patients often have an irritable carotid sinus.



Pressure over the sinus may not only slow the heart significantly but it may also inhibit inspiration. It is quite certain that there is a similar irritability of the reflexes originating from the arch of the aorta. These patients may have episodes of tachycardia precipitated by a change in their position from the horizontal to the vertical. They appear at times to be suffering from orthostatic hypotension. If one takes a circulation time during an episode of tachycardia it will be shortened. If, however, this is repeated under basal conditions at the same time as the metabolic rate a normal circulation time will be observed.

One may also be misled by the increase in the metabolic rate (25 to 35 per cent) when taken by the oxygen consumption method. If the respirations of these subjects are observed, they will be found to be irregular, at times quite shallow, and at other times unusually deep and sighing in character. This can be seen best on examination of the spirometer tracings taken while the subject is breathing oxygen. In the protocols of Goldbloom<sup>9</sup> it was noted that the respiratory quotients tended to be high. This would indicate that at times hyperventilation was occurring. The patients often have a subcyanotic color to the finger tips. Hick and associates<sup>10</sup> have found in some cases a definitely low oxygen saturation of the arterial blood. One can, therefore, understand that if a patient has a low oxygen saturation of hemoglobin, he would show an increased oxygen utilization when allowed to breathe oxygen. In this manner a false positive increased metabolic rate would be obtained.

The definitive diagnosis can usually be made by searching the patient's history for evidence of extra heat production, by studying the quantity of food eaten, the changes in his weight, and above all by looking for psychoneurotic episodes and causes for social maladjustment. With such information in hand one can critically re-interpret laboratory data. If, on reviewing these, an elevated or high normal blood cholesterol was discovered, one would be quite loath to make a diagnosis of hyperthyroidism.

#### BEHAVIOR OF THE CIRCULATION IN ESSENTIAL HYPERTENSION

In essential hypertension there is no increase in heat production. The peripheral blood flow is not increased and the cardiac output is normal or low.<sup>11</sup> The circulation time also is within normal limits unless decompensation is present.<sup>12</sup> Many patients develop anxiety states when they find that they have hypertension. Vasomotor instability appears and the metabolic rate is often elevated. In such cases one again must resort to a critical clinical study of the patient, repeated circulation times, and a study of the blood cholesterol values to arrive at a correct diagnosis. It is of course appreciated that patients with hypertension commonly develop hyperthyroidism. They will then show the diagnostic findings of hyperthyroidism.

## FACTORS CONTRIBUTING TO CIRCULATORY FAILURE IN HYPERTHYROIDISM

*Inadequate Nutrition of the Heart.*—The magnitude of the energy expenditure in a patient with severe hyperthyroidism who has not received adequate treatment is not commonly appreciated. If we assume that a normal subject with a basal energy expenditure of 1,500 calories develops hyperthyroidism with a metabolic rate of plus 75 per cent, his basal expenditure will be 2,625 calories. If he leads a sedentary life, his requirements will be basal plus 30 per cent (3,412 calories). If he does moderate work they will rise to basal plus 50 per cent (3,937 calories). Plummer and Boothby<sup>13</sup> have noted that the "cost of work" is greater in hyperthyroid than normal patients. This is due not only to unnecessary movements but also to the greater than normal oxygen consumption required for a given task. The patient's movements are excessive due to the tremor and he often spends a good portion of the night in extra activity tossing from one side of the bed to another. It is, therefore, safe to say that a patient with a hyperthyroidism of this severity attempting to work will have an energy expenditure nearer to 6,000 to 7,000 than 4,000 calories. If such a patient should be exposed to a spell of hot weather with a relatively high humidity then he would be crippled in eliminating heat. Some of it would be retained and this would cause a further increase in his energy expenditure.

It is quite a problem for a man to eat 7,000 calories of food. In the first place, it cannot be secured in the ordinary diet without definite planning to include large quantities of fat. Hence, the probability that the uninstructed individual would select this amount of food is small. Further, the fatigue and exhaustion from which he is suffering would reduce his appetite and increase the gastrointestinal irritability to preclude the possibility of his eating that quantity of food. Consequently, the patient develops a sharp deficiency in his caloric intake, and a state of semistarvation is established. The inroads of starvation are grossly recognized by the disappearance in the fat stores, and the atrophy of the muscles. He develops a negative nitrogen balance and the urine is found to contain creatin. These findings indicate that a rapid destruction of muscle tissue is occurring. As soon as extra food is taken the creatin disappears and the negative nitrogen balance is converted into a positive one. The positive nitrogen balance will be maintained for a long time. This persistence of a positive nitrogen balance following adequate caloric intake is also seen in the convalescent period of many infectious diseases, notably typhoid fever and tuberculosis. The tachycardia in infectious diseases is unrelieved by drug therapy, but it is slowly relieved by rest and diets adequate in all respects. It would seem that a state of starvation has a deleterious effect on the heart muscle. In accord with this conception is the reduction in glycogen content of heart muscle occurring in experimental

hyperthyroidism.<sup>14</sup> Cowgill and his associates<sup>15</sup> reported that the onset of symptoms of B deficiency occurred more rapidly in dogs treated with thyroxin than in untreated ones. Since that time evidence has rapidly accumulated<sup>16</sup> that the hyperthyroid patient requires more thiamine than the normal subject, that he probably is somewhat wasteful in his use of it, and that its concentration in his liver is subnormal. The preoperative use of supplementary doses of thiamine in thyrotoxic patients is now a routine procedure in many clinics. Attention<sup>17</sup> has been called to deficiencies of other members of the B complex group in severely toxic hyperthyroid patients. That thiamine deficiency may be responsible for anatomic changes in the heart muscle is indicated by studies in pigs. Pollis, Miller, Wintrobe, and Stein<sup>18</sup> have shown that their thiamine-deficient pigs die a cardiac death. They had labored breathing and cyanosis which was aggravated by exercise. Autopsy revealed edema of the lungs, cardiac dilatation, and focal necrosis in muscle fibers of the auricles and ventricles. In animals to which small amounts of thiamine were administered, widespread scarring of the musculature was observed.

#### CHANGES IN RATE AND RHYTHM

*Tachycardia.*—It is well known that an apparently normal heart subjected to a bout of paroxysmal tachycardia may develop failure as a result of the acceleration. During such periods of acceleration the output may be diminished as much as 33 per cent and at times the arterial pressure falls.<sup>19</sup> The filling of the ventricle is retarded by the short diastole and by the contraction of the auricle while the ventricle is still insystole. The decrease in diastole and the drop in aortic pressure renders the coronary circulation less efficient. Starling and Visscher<sup>20</sup> using the heart-lung preparation have shown that acceleration in rate diminishes the mechanical efficiency of the heart. In hyperthyroidism moderate increases in rate can be attributed to the increased blood volume and filling of the heart as described by Bainbridge.<sup>21</sup> In the faster tachycardias there are other factors operative, which cannot be regarded as physiologic. These are the increased thyroxin content of the heart muscle, and exhaustion. One can now appreciate the statistical reason for the poor prognosis in patients with excessively rapid heart rates. One should not indulge in optimism because of the absence of signs of failure. An elevated venous pressure is beneficial since it facilitates the filling of the heart and increases the cardiac output. These rapid hearts with normal venous pressures are quite vulnerable to acute failure. It is highly probable that sudden anesthetic deaths occasionally seen in hyperthyroid patients, who were apparently well compensated, are attributable to this mechanism.

*Auricular Fibrillation.*—A bout of paroxysmal fibrillation has a definite adverse effect on the heart. The cardiac output may be reduced as

much as 25 to 30 per cent,<sup>22</sup> due to the reduction in the blood contributed by the auricular systole. The venous pressure is normal and is unable to compensate for the auricular failure. The conductivity of the bundle of His is unimpaired and so the ventricular rate tends to follow that of the auricles. The diastole shortens, the heart muscle becomes fatigued, the coronary flow inadequate, and the pulse deficit greater. Fortunately one has available in quinidine a drug effective in restoring normal rhythm. This drug should be used promptly and given in doses sufficient to abolish the fibrillation. Conditions are somewhat different in patients with chronic fibrillation. They are frequently comfortable and may be oblivious of their cardiac irregularity. Their behavior is in sharp contrast to the uncomfortable and disturbed state of the patient with a bout of paroxysmal fibrillation. In chronic fibrillation there is usually cardiac decompensation of sufficient degree to elevate the venous pressure, which insures filling of the ventricles and compensates for the loss of auricular systole. In the elderly patient with arteriosclerosis there is already some impairment in conductivity of the bundle of His. The ventricular rate is correspondingly slowed and the pulse deficit is not so great.

*Auricular Flutter.*—The same situation prevails as in fibrillation. If the ventricles should follow the auricular rate a serious circulatory collapse would result because of the great reduction in cardiac output. Usually the refractory phase of the conducting tissues is longer than that of the auricle and thus a heart block with a 2 to 1, 3 to 1, or 4 to 1 rhythm is established. The reduction in the ventricular rate enables the heart to function reasonably satisfactorily. The paroxysmal attacks of flutter which occur postoperatively are most disabling and should be treated as emergencies.

It is much safer to treat flutter with digitalis than quinidine. Adequate doses of digitalis should increase the auriculoventricular block, slow the ventricle, and save the patient's life. It may convert the flutter into fibrillation by stimulation of the vagus. This shortens the refractory period of the auricular muscle, increases the transmission rate, and speeds up the revolutions of the circus wave, thus converting the flutter into fibrillation. When the drug is stopped the fibrillation is often replaced by a normal rhythm. Theoretically, quinidine should convert the flutter into normal rhythm by retarding conduction within the auricular muscle and increasing the refractory period. Practically this action is by no means certain and dependence should not be placed in it in such a grave emergency.

*Heart Failure.*—Heart failure is a complication that can be expected in patients with long-standing hyperthyroidism. When the severity of the hyperthyroidism is increased, failure appears more rapidly. The onset is usually slow and insidious. The factors leading to failure are operative on both the right and left heart. The clinical picture is that of congestive failure with dependent edema, large liver, and

hyperthyroidism.<sup>14</sup> Cowgill and his associates<sup>15</sup> reported that the onset of symptoms of B deficiency occurred more rapidly in dogs treated with thyroxin than in untreated ones. Since that time evidence has rapidly accumulated<sup>16</sup> that the hyperthyroid patient requires more thiamine than the normal subject, that he probably is somewhat wasteful in his use of it, and that its concentration in his liver is subnormal. The preoperative use of supplementary doses of thiamine in thyrotoxic patients is now a routine procedure in many clinics. Attention<sup>17</sup> has been called to deficiencies of other members of the B complex group in severely toxic hyperthyroid patients. That thiamine deficiency may be responsible for anatomic changes in the heart muscle is indicated by studies in pigs. Folliis, Miller, Wintrobe, and Stein<sup>18</sup> have shown that their thiamine-deficient pigs die a cardiac death. They had labored breathing and cyanosis which was aggravated by exercise. Autopsy revealed edema of the lungs, cardiac dilatation, and focal necrosis in muscle fibers of the auricles and ventricles. In animals to which small amounts of thiamine were administered, widespread scarring of the musculature was observed.

#### CHANGES IN RATE AND RHYTHM

*Tachycardia.*—It is well known that an apparently normal heart subjected to a bout of paroxysmal tachycardia may develop failure as a result of the acceleration. During such periods of acceleration the output may be diminished as much as 33 per cent and at times the arterial pressure falls.<sup>19</sup> The filling of the ventricle is retarded by the short diastole and by the contraction of the auricle while the ventricle is still insystole. The decrease in diastole and the drop in aortic pressure renders the coronary circulation less efficient. Starling and Visscher<sup>20</sup> using the heart-lung preparation have shown that acceleration in rate diminishes the mechanical efficiency of the heart. In hyperthyroidism moderate increases in rate can be attributed to the increased blood volume and filling of the heart as described by Bainbridge.<sup>21</sup> In the faster tachycardias there are other factors operative, which cannot be regarded as physiologic. These are the increased thyroxin content of the heart muscle, and exhaustion. One can now appreciate the statistical reason for the poor prognosis in patients with excessively rapid heart rates. One should not indulge in optimism because of the absence of signs of failure. An elevated venous pressure is beneficial since it facilitates the filling of the heart and increases the cardiac output. These rapid hearts with normal venous pressures are quite vulnerable to acute failure. It is highly probable that sudden anesthetic deaths occasionally seen in hyperthyroid patients, who were apparently well compensated, are attributable to this mechanism.

*Auricular Fibrillation.*—A bout of paroxysmal fibrillation has a definite adverse effect on the heart. The cardiac output may be reduced as

Oxygen should be used until the pulmonary engorgement is relieved. After a patient is well along toward compensation he enjoys being liberated from the oxygen. He will usually be quite comfortable in the day, but he will find difficulty in securing a night's sleep from which he awakens refreshed. This is an indication for the continuation of oxygen during the night. Sedatives and opiates will be required and should be given as needed.

Digitalis should be used in therapeutic doses, when heart failure exists. If the failure is associated with chronic fibrillation it is still the drug of choice. If heart failure is precipitated by a bout of paroxysmal fibrillation, then quinidine should be given, by mouth or per rectum (when vomiting is present), at frequently repeated intervals until the normal rhythm is restored. If restoration of normal rhythm is delayed by decompensation, then digitalis should be given in addition to the quinidine.

The edema of the tissues often disappears slowly under the best of treatment. Its increase is associated with an aggravation of the symptoms of dyspnea. Its decrease brings a corresponding relief. In patients with long-standing hyperthyroidism one should consider that there is a definite nutritional basis for the edema even though the serum proteins may be normal. The protein in the diet should be increased. The patient should then be given intramuscularly, on alternate days, 2 c.c. of liver extract (two units to 1 c.c.) and 50 mg. of thiamine chloride. The thiamine stimulates the appetite and corrects the thiamine deficiency. The liver extract seems to assist in correcting other deficiencies. Ammonium chloride alone or combined with an intravenous injection of one of the mercurial diuretics (at four-day intervals) should be given, providing there is no increase in the nonprotein nitrogen in the blood. In giving the mercurial diuretic it is well to dilute it with 10 c.c. of water or 5 per cent glucose solution. This avoids troublesome attacks of thrombophlebitis. When there is a retention of nitrogen one must proceed more cautiously. The retention of nitrogen may be due to passive congestion of the kidneys and it may disappear when the circulation is improved. While one is waiting for the oxygen, digitalis, and other measures to become effective, ammonium chloride alone can be given a trial. If the results are disappointing, then aminophyllin in 0.5 Gm. doses daily, dissolved in from 300 to 500 c.c. of 10 per cent glucose in distilled water, may be given slowly intravenously. The aminophyllin prevents the resorption of water by the tubules. However, its effect is not toxic and a damaged kidney does not become crippled further in its use as it does when a mercurial diuretic is administered. Aminophyllin dissolved in hypertonic glucose solution has a favorable effect on the pulmonary edema and the associated bronchospasm. Finally, the administration of the drug in a dilute form prevents annoying palpitation of the heart.

## CRITERIA OF COMPENSATION

*Enumeration of a Few Objective Criteria of Compensation.*—The physical examination should show the absence of signs of decompensation.

Hidden edema should be removed. If present in the lungs, it predisposes to atelectasis and bronchopneumonia. Since it is customary to have the patient out of bed prior to his operation, this will afford an opportunity for the fluid to accumulate in the feet. The skin on the arms and other parts of the body feels thick when edema is present. In all cases the patient should be subjected to diuresis. This is done by weighing him daily over a period of time and collecting daily his specimens of urine. During this period he can be given ammonium chloride and a mercurial diuretic. The amount of diuresis and the weight variations will readily reveal the presence or absence of edema.

If the venous pressure is elevated one can be quite certain that the patient still has right heart failure. If the venous pressure is normal then the right heart is competent.

The arm-to-tongue circulation time should not be prolonged excessively. However, the circulation through the pulmonary spaces may be slowed without actual stasis. Consequently, one should not insist that this value be a normal one.

The final test of compensation is the vital capacity. If this has a value of 70 per cent or more one can feel that there is no pulmonary edema and that the expansion of the alveoli is not embarrassed. A vital capacity which is inadequate in a patient who otherwise appears in good condition can be improved by diuresis induced with ammonium chloride and a mercurial diuretic. If this is not effective a return to oxygen at night for a few days will often prove beneficial. One would not wish to create the impression that a patient may not be operated upon who has a vital capacity below 70 per cent. Obviously, clinical judgment and other studies will dictate the proper course to be followed.

## REFERENCES

1. Wollheim, E.: Die zirkulierende Blutmenge und ihre Bedeutung für Kompensation und Dekompensation des Kreislaufs, *Ztschr. f. klin. Med.* 116: 269-397, 1931.
2. Meek, W. J., and Eyster, J. A. E.: 'Effect of Plethora and Variations in Venous Pressure on Diastolic Size and Output of Heart, *Am. J. Physiol.* 61: 186-202, 1922.
3. Hardy, J. D.: The Physical Laws of Heat Loss From the Human Body, *Proc. Nat. Acad. Sc.* 23: 631-637, 1937.
4. Keeton, R. W., Hick, F. K., Glickman, N., and Montgomery, M. M.: The Influence of \_\_\_\_\_ on Comfort Requirements, *Tr. Am. Soc. Heating & V* 47: 159-174, 1941.
5. Stewart, H. J., \_\_\_\_\_ Peripheral Blood Flow in Myxedema as Compared With That in Hyperthyroidism, *Am. Heart J.* 23: 175-184, 1942.
6. Glickman, N., Hick, F. K., Keeton, R. W., and Montgomery, M. M.: Blood Volume Changes in Men Exposed to Hot Environmental Conditions for a Few Hours, *Am. J. Physiol.* 134: 165-176, 1941.
7. Gibson, J. G. Jr., and Harris, A. W.: Clinical Studies of Blood Volume; Hyperthyroidism and Myxedema, *J. Clin. Investigation* 18: 59-65, 1939.

8. Lewis, J. K., and McEachern, D.: Persistence of Accelerated Rate in Isolated Hearts of Thyrotoxic Rabbits; Response to Iodides, Thyroxine and Epinephrine, *Bull. Johns Hopkins Hosp.* 48: 228-241, 1931; Abstr., *Proc. Soc. Exper. Biol. & Med.* 28: 501-506, 1931.
- Yater, W. M.: Tachycardia, Time Factor, Survival Period and Seat of Action of Thyroxine in Perfused Hearts of Thyroxinized Rabbits, *Am. J. Physiol.* 98: 338-343, 1931.
- Yater, W. M.: Mechanism of Adjustment of Circulation in Hyperthyroidism (Thyrotoxicosis), *Am. Heart J.* 8: 1-7, 1932.
9. Goldbloom, A. A.: Diagnostic Importance of Blood Volume and Cardiac Output Studies in a Borderline Case of Thyrotoxicosis, *M. Clin. North America* 17: 279-295, 1933.
10. Hick, F. K., Christian, A. W., and Smith, P. W.: Criteria of Oxygen Want, With Especial Reference to Neurocirculatory Asthenia, *Am. J. M. Sc.* 194: 800-804, 1937.
11. Burwell, C. S., and Smith, W. C.: Output of Heart in Patients with Abnormal Blood Pressures, *J. Clin. Investigation* 7: 1-10, 1929.
- Ringer, M., and Altschule, M.: Studies on Circulation; Cardiac Output in Diseases of Heart, and Under Influence of Digitalis Therapy, *Am. Heart J.* 5: 305-343, 1930.
- Weiss, S., and Ellis, L. B.: Quantitative Aspects and Dynamics of Circulatory Mechanism in Arterial Hypertension, *Am. Heart J.* 5: 448-468, 1930.
12. Blumgart, H. L., and Weiss, S.: Studies on Velocity of Blood Flow; Velocity of Blood Flow and Its Relation to Other Aspects of Circulation in Patients With Arteriosclerosis and in Patients With Arterial Hypertension, *J. Clin. Investigation* 4: 173-197, 1927.
13. Plummer, H. S., and Boothby, W. M.: The Cost of Work in Exophthalmic Goiter, *Proc. Am. Physiol. Soc., Am. J. Physiol.* 63: 406, 1922.
14. Andrus, E. C.: The Heart in Hyperthyroidism; A Clinical and Experimental Study, *Am. Heart J.* 8: 66-74, 1932.
15. Himwich, H. E., Goldfarb, W., and Cowgill, G. R.: Studies in Physiology of Vitamins; Effect of Thyroid Administration Upon Anorexia Characteristic of Lack of Undifferentiated Vitamin B, *Am. J. Physiol.* 99: 689-645, 1932.
16. Editorial: Thiamine Deficiency in Hyperthyroidism, *J. A. M. A.* 123: 1049, 1943.
17. Williams, R. H., Egana, Eurique, Robinson, P., Asper, S. P., and Dutort, C.: Alterations in Biologic Oxidation in Thyrotoxicosis; Thiamine Metabolism, *Arch. Int. Med.* 72: 353-371, 1943.
18. Follis, R. H., Jr., Miller, M. H., Wintrobe, Maxwell, and Stein, H. J.: Development of Myocardial Necrosis and Absence of Nerve Degeneration in Thiamine Deficiency, *Am. J. Path.* 19: 341, 1943.
19. Barcroft, J., Bock, A. V., and Roughton, F. J.: Observations on the Circulation and Respiration in a Case of Paroxysmal Tachycardia, *Heart* 9: 7-13, 1921.
20. Starling, E. H., and Visser, M. B.: Regulation of Energy Output of Heart, *J. Physiol.* 62: 243-261, 1927.
21. Bainbridge, F. A.: The Effect of Venous Filling Upon the Rate of the Heart, *J. Physiol.* 50: 65, 1915.
22. Smith, W. C., Walker, G. L., and Alt, H. L.: Cardiac Output in Heart Disease; Complete Heart Block, Auricular Fibrillation Before and After Restoration to Normal Rhythm, Subacute Rheumatic Fever and Chronic Rheumatic Valvular Disease, *Arch. Int. Med.* 45: 706-726, 1930.
- Kerkhof, A. C.: Minute Volume Determinations in Mitral Stenosis During Auricular Fibrillation and After Restoration of Normal Rhythm, *Am. Heart J.* 11: 206-211, 1936.
23. Lahey, F. H.: End Results in Thyrocardiacs, *Am. J. Surg.* 90: 750-755, 1929.
24. Pemberton, J. De J.: Goiter; Management of Poor Surgical Risk, *Arch. Surg.* 20: 591-606, 1930.



# THE MEDICAL MANAGEMENT OF THYROTOXICOSIS

DAVID P. BARR, M.D., NEW YORK, N. Y.

*(From the Department of Medicine, Cornell University Medical College and the New York Hospital)*

**I**N RECENT years the control of thyrotoxicosis has been chiefly dependent upon three expedients: the use of iodine, exposure of the thyroid gland to x-ray, or surgical extirpation of a large part of the thyroid parenchyma. Although the approach has been by diverse routes, the therapeutic aims of all methods have been similar and the differences in effect have been quantitative rather than qualitative. Success in each instance has depended upon a diminution in the amount of circulating thyroid hormone with the expectation that thereby clinical manifestations of the disease would be minimized or removed.

Improvement has been evaluated by a number of criteria. The most emphasized has been a reduction in the basal metabolic rate which should be accompanied by a gain in weight, a diminution in the tachycardia, a decrease in pulse pressure, and amelioration of the abnormally high circulation rate. It is usually assumed that these symptoms are accompaniments of, or compensations for, the increased oxidative rate.

Improvement may also be evaluated by change in signs which are not so obviously dependent upon the degree of metabolic activity. Among these should be included the tremor, sweating, irritability, hyperkinesis, and exophthalmos. There should also be correction of the tendency to loss of nitrogen, calcium, and phosphorus from the body and an increase in the level of cholesterol in the plasma.

The muscular weakness which is so characteristic of chronic thyrotoxicosis should become less evident and with this benefit there should be an improvement in the spontaneous creatinuria, the inability to store ingested creatin and the abnormally high creatinin excretion which characterizes the disease.

The abnormality in creatin metabolism has been sufficiently constant to justify the use of spontaneous creatinuria and creatin tolerance tests as diagnostic criteria in cases which offer difficulty in differentiation between hyperthyroidism and psychoneurosis.<sup>1</sup> This has been especially useful since not infrequently the creatin defect has been evident when the basal is within normal limits. The tests have also been helpful in studying patients whose symptoms have not been satisfactorily controlled by thyroidectomy. Here again the creatin excretion may be excessive during periods when the basal metabolic rate is within the rather wide limits of normal.

When the preceding criteria are used in evaluating therapeutics by means of iodine, radiation, or surgery, the results are similar in that all of the agents tend to ameliorate all of the disturbed functions. The mechanisms involved and the degree of benefit vary greatly. Apparently iodine exerts its influence by increasing the storage of active organic iodine compounds. The optimal benefits are temporary and alone seldom constitute a satisfactory means of control. Surgical operation accomplishes benefit by removing a large part of the mechanism which produces the hormone. Considering the fact that the amount to be removed must be determined by guess, subtotal thyroidectomy has been, and is, a surprisingly satisfactory procedure. Radiation is effective because of injury to the structure of the gland or of a temporary diminution in its function. While radiation has been in the past less helpful than surgery the possibilities of newer applications in the form of radioactive iodine have not been sufficiently explored. Hertz and associates<sup>2</sup> and Hamilton<sup>3</sup> have shown a selective action of radioactive iodine in hyperplastic portions of thyrotoxic glands and, in a few cases, have obtained by its use encouraging therapeutic results.

Another mechanism of reducing the production or delivery of thyroid hormone should be mentioned although it can not be feasibly employed in treating hyperthyroidism. The ablation, destruction, or loss of the anterior lobe of the pituitary removes the stimulus to functional thyroid activity. Results are a small thyroid gland in which the cells are atrophic and simultaneously a great reduction in the level of circulating thyroid hormone. In this state the thyroid gland is by no means destroyed and for at least a considerable period its function can be restored by appropriate stimulation with the thyrotropic hormone of the pituitary.

Still another method by which the amount of thyroid hormone may be reduced has been shown by Means and others<sup>4</sup> in the hyperplasia of the thyroid gland and the paradoxical hypothyroidism which follows the administration of thiocyanate, and which is prevented by the administration of iodine.

Of the expedients which have been available in the treatment of thyrotoxicosis, partial surgical ablation of the thyroid gland has offered most hope. With the best preparation and in the hands of excellent surgeons the operative risk has been diminished to less than 1 per cent with recurrence of clinical hyperthyroidism in only 10 to 15 per cent of the patients operated upon. This remarkable record can be attributed only in part to increase in surgical skill. Better understanding of thyrotoxicosis and appropriate emphasis upon control of physical activity, freedom from emotional strain, iodine, and adequate diet have contributed significantly to successful management. While all of these factors are important in any phase of treatment they have been used more in preparation for operation than as ends in themselves.

## CONTROL OF PHYSICAL ACTIVITY

If partial thyroidectomy is contemplated, a thyrotoxic patient should be under constant observation and preferably in a hospital for at least two weeks preceding the operation. Effective rest and relaxation are necessary in the treatment of hyperthyroidism. The thoroughness with which they must be enforced, however, varies with the age and the general condition of the patient as well as with the degree of thyrotoxicosis. The young previously healthy individual has such large factors of safety that even hard work and the unmodified stress of life may cause no obvious distress. The effects of fatigue, however, are cumulative and strains which do not make their effect evident at once may cause later trouble. It should be the rule to spare the hyperthyroid patient all unnecessary stress until his condition can be permanently remedied. While this is, to a certain extent, optional in the younger individual, it becomes obligatory in those whose hearts have lost, with the passage of the years, some of their initial reserve or in those in whom the degree of hyperthyroidism threatens the occurrence of a crisis. It applies to all thyrotoxic patients during infection or subsequent to psychic or physical trauma.

Appropriate relaxation is by no means easy of accomplishment. In many ambitious, restless, thyrotoxic patients complete inactivity is out of the question and attempts to enforce it in the solitude of darkened rooms, or in other respects too literally, may be among the principal causes of failure in medical management. Recumbency is by no means essential. In the most severe cases, when strict bed rest is necessary, the bed should be adjusted frequently by the attendant so that the patient may assume the most comfortable position for each permitted activity. Even in the very ill, the avoidance of boredom is more important than complete quiescence. Activities may be prescribed according to the taste of the patient and may include short periods of reading, listening to the radio, visiting, or performing some of the simpler, easier tasks offered by occupational therapists. In prescribing activity, strict limits must be placed on the time allowed for each item and it must be emphasized that there is no obligation to complete any task.

Periods of complete rest and relaxation should be frequent but need not be prolonged except in those whose hearts are seriously incompetent. In the less severe cases much more liberty is permissible as long as its effect can be accurately observed. Indeed, in the preoperative period the effect of walking on pulse, blood pressure, and respiration may offer a valuable indication as to the ability of the patient to withstand the strain of the operation.

## REASSURANCE

Too much emphasis cannot be placed on psychologic factors in the management of thyrotoxicosis. Patients are irritable, excitable, restless,

and hyperkinetic but usually are astonishingly free from imaginary fears. On the other hand they are susceptible to suggestion and are influenced to an unusual degree by the mood of a physician. An attitude of gloom or uncertainty may be disastrous while optimism and assurance often have dramatically beneficial effects. As soon as acquaintanceship has been established, the main characteristics of the disease may be detailed to the patient. Emphasis must be placed on curability but also on the fact that the complete recovery may require time and that arrangements must be made for a prolonged period of inactivity. Helpfulness concerning these arrangements goes far in reassuring the patient. Thyrotoxic individuals who show no undue anxiety over their physical condition may become dangerously disturbed when they contemplate the consequences of illness on their financial security or on their dependents. While formal attempts at psychotherapy may be quite inadvisable during the preoperative period, an understanding of factors and problems which prevent relaxation is essential. Even when the causes of worry can not be removed, a sympathetic and helpful attitude on the part of the physician exerts a significant therapeutic effect.

In most cases the question of operation can be discussed quite fully. Emphasis should be laid upon the relatively slight risk of operation and the relatively high incidence of resultant permanent cure. It is also important to emphasize that operation will not be attempted if the risk is great. The operation can be represented as a goal which the patient may achieve if he can relax enough and can establish a satisfactory state of nutrition.

#### CONTROL OF RESTLESSNESS

Restlessness may interfere seriously with treatment during the preoperative period. Its control will depend in large part upon reassurance, the prevention of boredom, and a thorough understanding of the patients' problems and attitudes. In some cases, however, restlessness and insomnia persist in spite of the most intelligent management. In such cases morning sponge baths at a temperature of about 80° F. and evening sponge baths at a temperature of from 90 to 95° F. may be helpful. For those who are less ill, an evening tub bath at a temperature of from 98 to 100° F. may be prescribed as a means of combating sleeplessness. An ice bag over the heart and over the thyroid gland may be used as a measure of subjective relief in those who are made restless by palpitation. While thyrotoxic individuals are not often unduly disturbed by sounds and lights, protection by isolation may be indicated for individual patients.

When restlessness can not be controlled by such simple measures, phenobarbital may be given in doses of from 15 to 30 mg. four times each day. If insomnia is a troublesome factor the night dose may be

increased to 60 or even to 90 mg. or a comparable dose of a shorter acting barbiturate such as pentobarbital may be tried. Both paraldehyde and chloral hydrate are at times useful as temporary substitutes for the barbiturates. Large doses of sedatives are seldom if ever indicated and may cause confusional states which are difficult to control and occasionally dangerous.

#### DIET

Undernutrition often plays an important role in chronic thyrotoxicosis. With maximum relaxation a thyrotoxic patient with a basal metabolic rate of plus 60 is expending as much energy as a normal person would require to sweep a floor. This activity must be maintained day and night and day after day. Moreover, all muscular work is performed inefficiently. Accurate observations have indicated that in performance of a given task thyrotoxic patients require approximately 40 per cent more energy than a normal person.<sup>5</sup> Roughly the caloric requirement during bed rest in such a degree of thyrotoxicosis may be calculated to be at least twice normal.

In hyperthyroidism there is always a tendency to depletion of glycogen which is demonstrable in the liver and may be a significant factor in the heart muscle and other tissues. For this reason a high carbohydrate intake is advisable. Excessive amounts of fat, on the other hand, are undesirable because they tend to produce diarrhea. An allowance of 1 Gm. of protein per kilogram of body weight is usually sufficient to prevent nitrogen loss if a sufficient caloric intake is maintained. Larger amounts may be regarded as somewhat undesirable because of the relatively high specific dynamic action of protein.

All thyrotoxic patients tend to lose calcium and therefore to require more than the normal intake of lime salts. The observations of Cowgill and Palmieri<sup>6</sup> have shown that the requirements of thiamine are proportional to the amount of food metabolized. This suggested at once that disturbances in thiamine metabolism might develop in thyrotoxicosis, and the work of Means and associates,<sup>7</sup> and Williams and others<sup>8</sup> has demonstrated that the administration of thiamine is of distinct advantage as an adjunct in the treatment of thyrotoxicosis. More recently, Drill and Overman<sup>9</sup> have shown that during experimental hyperthyroidism an increased intake of pyridoxine and pantothenic acid is required in order to maintain normal nutrition.

These factors must be taken into account in prescribing a diet during the preoperative period or at other times in the treatment of hyperthyroidism. For a small girl weighing 110 pounds, a diet containing carbohydrate 300 Gm., protein 50 Gm., and fat 275 Gm., would represent a satisfactory approximation at the beginning of treatment. This should include the use of one quart of milk each day and should be reinforced by the daily administration of from 10 to 20 mg. of thiamine hydro-

chloride and yeast or other vitamin supplements which will increase materially the usual intake of pyridoxine and pantothenic acid. Since the caloric needs of each patient can not be calculated exactly, daily weight must be used as the best indication of the sufficiency of any given diet.

#### IODINE

Appropriate use of iodine has saved the lives of thousands of thyrotoxic patients and since 1923<sup>10</sup> has been regarded as essential in the preoperative treatment of Graves' disease. Its beneficial effect depends upon the specific need of the thyrotoxic individual and when the need has been satisfied by increased intake the administration of larger amounts results in no perceptible added benefit. In thyrotoxic patients who have received no iodine other than that contained in a usual diet, the exhibition of the drug results in a characteristic and usually predictable response. This may be discernible in twenty-four hours, obvious in three or four days, and maximum in ten to fourteen days. Rather dramatic improvement in the clinical manifestations of Graves' disease is accompanied by changes in the structure of the thyroid gland. Continued use of iodine may or may not be accompanied by intensification of thyroid symptoms. Discontinuance of iodine on the other hand is followed by a gradual ascent of the basal metabolic rate to its previous level and by an increase in thyrotoxic symptoms to a severity which approximates that obtaining before iodine was given. About 3 per cent<sup>11</sup> of patients with Graves' disease do not respond to iodine.

The amount of iodine required to produce an optimal response is small and may vary between 6 and 15 mg. per day in different individuals with Graves' disease.<sup>12</sup> Many compounds containing iodine are known to be effective and the response seems to be equally favorable from inhalations of ethyl iodide and from oral administration of diiodotyrosine, potassium iodide, hydriodic acid, or Lugol's solution.<sup>11</sup> One cubic centimeter of syrup of hydriodic acid containing about 13 mg. of iodine, or 2 minims of Lugol's solution containing approximately 18 mg. of iodine should be all that is required for each day's treatment.

Ordinarily it is calculated that the optimum effect of iodine should develop in from ten to fourteen days following its first exhibition. This should not be taken too literally. It is the condition of the patient and not the interval that must determine the time of operation.

#### USE OF DIGITALIS

The state of the circulation during the preoperative period must be carefully observed. Tachycardia and moderate grades of cardiac incompetence are best controlled by rest and iodine. Digitalis is indicated whenever there is obvious congestive heart failure or in cases of auricular fibrillation with very rapid pulse rate or continued or large pulse deficit. In such cases the drug should be started early in the preoperative

period in order that its benefits may be achieved and its possible toxic effects controlled before the time of operation. Statistical evidence indicates that the routine administration of large doses of digitalis is detrimental and actually increases the mortality from surgical procedures. Tachycardia with regular rhythm and without cardiac decompensation is never an indication for the use of digitalis.

#### INDICATIONS AND CONTRAINDICATIONS FOR OPERATION

After two weeks of controlled activity, psychotherapy, iodine administration, and dietotherapy it is hoped that a patient will be in sufficiently good condition to justify subtotal thyroidectomy. Not all cases can be so managed. Certain contraindications should be mentioned. It has been noted that those who respond unsatisfactorily or not at all to iodine have a relatively high operative mortality. A rising metabolic rate after an initial favorable response should also be viewed with some apprehension. A basal metabolic rate higher than plus 40 is usually regarded as unfavorable although it must be emphasized that basal rates are to be evaluated in relation to other clinical manifestations. Failure to maintain weight with or without vomiting or diarrhea during the preoperative period is to be regarded as an unfavorable sign and often a contraindication to immediate operation. The coincidence of infection of any sort, acute worry, grief, emotional storms, and psychoses increase the risk to such an extent that immediate operative procedures cannot be considered. Old age in itself is not a sufficient reason for depriving a patient of the benefits of thyroidectomy but accompanying degenerative diseases may in many cases render any thyroid surgery somewhat futile. Congestive heart failure which has been uncorrected by rest, iodine, and digitalis may preclude any immediate operation. In deciding about such cases, however, it must be remembered that thyroidectomy is often followed by almost complete recovery even from rather advanced failure. For this reason, repeated effort by all therapeutic methods should be made to attain temporary improvement which may permit operation.

#### NONSURGICAL MANAGEMENT OF CHRONIC THYROTOXICOSIS

Those patients who for one reason or another cannot be subjected to subtotal thyroidectomy must be treated by other methods. In the nonsurgical management two factors are perhaps outstanding. The first is that the condition of thyrotoxicosis undergoes wide spontaneous fluctuations in severity with periods of remission and relapse which are more or less obviously influenced by emotional states and infections, as well as by the menstrual cycle and pregnancy. The second is that the administration of an appropriate amount of iodine modifies the extent of the fluctuations and usually prevents the serious consequences of acute hyperthyroidism during relapse. These characteristics indicate

the importance of protection from those factors which may be preventable, and the advisability of continuous use of such small amounts of iodine as are necessary to maintain an optimal state of the thyroid gland.

With the best management, however, results have not been very satisfactory. While remissions with periods of moderately good health have been common, cure in the sense of removing the tendency to relapse has been decidedly rare. Moreover, the continuance of even a moderate degree of hyperthyroidism produces circulatory strain which, with advancing years and diminishing cardiac reserve, produces obvious thyrotoxic heart disease. In such cases the persistent cautious use of x-ray has resulted in much benefit and has proved itself next to operation the most potent weapon in the permanent control of the condition.<sup>13</sup>

#### THIOURACIL

Although the results of surgery have been brilliant indeed and although the x-ray has been instrumental in the successful control of many cases, it is apparent that all of the present means of treating thyrotoxicosis leave much to be desired. None achieves the ultimate goal of a therapeutic agent which without mutilation, destruction, or disturbance of function of other organs can check the production or prevent the delivery of excessive amounts of thyroid hormone.

Interest in the possibility of finding a more ideal agent was stimulated by the discovery of the McKenzies and McCollum<sup>14</sup> that prolonged administration of sulfaguanidine produced hyperplasia of the thyroid gland which, like thiocyanate, decreased the basal metabolic rate to levels approaching myxedema. Unlike thiocyanate, the effect could not be prevented by iodine. On the other hand its action might be obviated by giving thyroxin. The work of the McKenzies was extended by Richter and Clisby<sup>15</sup> and by Kennedy<sup>16</sup> to show that an effect similar to that of sulfaguanidine could be produced by compounds containing the thioureyline radical and particularly by thiourea and its derivatives. Extensive studies by Astwood<sup>17</sup> with over 100 related compounds revealed that the most marked effects could be obtained with thiouracil. In animals Astwood was able to show that glands subjected to prolonged administration of thiourea and its derivatives became enlarged with follicles irregular in shape, containing scant colloid and lined by columnar cells with large nuclei and numerous mitoses.<sup>18</sup> The administration was followed after a short interval by a lowering of the basal oxygen consumption, a decrease in growth, and a diminished food intake. The obvious question whether these substances would have an effect in human thyrotoxicosis was approached by Astwood and by Williams and Bissell.

Astwood<sup>19</sup> treated two patients, one of whom received thiourea and the other thiouracil. In both there was a fall in metabolic rate and



an increase in body weight. The more extensive studies of Williams and Bissell<sup>20</sup> concerned nine patients who were treated with thiouracil. All had had typical manifestations of thyrotoxicosis over periods from six months to twenty-two years. In most instances the thyroid glands were enlarged. Initial basal metabolic rates ranged from plus 36 to plus 88. In all cases the basal had returned to normal with an average of plus 1 for the group within from three to seven weeks following institution of treatment. In four weeks there was a decrease in the protein-bound iodine of the plasma to normal or below. Williams showed also that administration of thiouracil did not interfere with the predicted effect of 1.5 Gm. of desiccated thyroid in two cases of myxedema. His observations confirmed animal experiments which indicated that thiouracil does not interfere with the action of preformed thyroxin.

These preliminary observations showed the remarkable effect of thiouracil on the basal metabolic rate. From both theoretical and practical standpoints it was of great interest to inquire whether the fall in oxidative rate was accompanied by the changes which are ordinarily employed as criteria for good therapeutic results from iodine, radiation, or surgical treatment. The question was pertinent since it is well known that the variations in basal metabolic rate encountered in fever, in leucemia, in Addison's and Fröhlich's diseases, and in dinitrophenol poisoning are not necessarily accompanied by other metabolic and circulatory changes which characterize variations in activity of the thyroid gland. It would not be impossible that the effect of thiouracil on oxidative rate might be accomplished by some mechanism other than by diminishing the amount of circulating thyroid hormone.

Observations made by Sloan and Shorr<sup>21</sup> demonstrated that thiouracil produces changes in circulation rate, pulse rate, blood pressure, calcium and nitrogen balance, creatin metabolism, and cholesterol levels which were qualitatively identical with those achieved by the successful use of iodine, x-ray, or thyroidectomy. The effects of the drug are physiologic in the sense that it tends to correct those functions which are disturbed or exaggerated in thyrotoxicosis.

The effects of thiouracil are now being studied in many clinics. It has been found in the great majority of cases of Graves' disease that freedom from thyrotoxic symptoms may be attained by a few weeks of intensive treatment with thiouracil and that essentially normal conditions may be maintained indefinitely by administration of small amounts of the drug. It has also been shown in a few cases by Astwood<sup>22</sup> that withdrawal of the drug after six to nine months of treatment does not result in recurrence of thyrotoxicosis. Unfortunately, it has also been found that thiouracil possesses toxic properties. Granulocytopenia, early noted by Astwood,<sup>19</sup> has resulted in several deaths, one of which has been reported.<sup>23</sup> Use of the drug has also been followed not infrequently by eruptions<sup>2</sup> and by periods of pyrexia.<sup>24</sup>

It is too early to predict whether thiouracil can be employed safely in the routine management of thyrotoxicosis. Present evidence is not sufficient to exclude possible hidden toxic reactions which might result from its continued use. At the moment its employment should be restricted to cautious administration in well-selected cases under constant observation. It may not be too much to hope, however, that there will be found closely related drugs which possess its favorable actions without its toxic side effects.

#### SUMMARY

Medical treatment of thyrotoxicosis has found its rationale in our present concepts of its nature. It is based first on the understanding that the disease is aggravated by infections, by physical and emotional stress, and by such variations in function of the endocrine system as occur at the time of puberty and during menstruation and pregnancy; second, on the observation that relapses may be modified or minimized by the administration of relatively small amounts of iodine. Adequate diet, reassurance, control of activity and of restlessness, protection against infections and against physical and psychologic trauma, and the feeding of small amounts of iodine have constituted the mainstays of medical treatment. These expedients have been used chiefly as a preparation for surgery or when this has been impossible as ancillary to cautious, persistent application of x-rays. When used by themselves they have not been successful in curing or controlling effectively many cases of thyrotoxicosis.

The recent introduction of thiouracil offers new hope of more effective medical control and suggests the possibility that the use of thiouracil or related compounds may permit nonsurgical treatment in a large number of thyrotoxic patients.

#### REFERENCES

1. Richardson, H. B., and Shorr, E.: The Creatin Metabolism in Atypical Graves Disease, *Tr. A. Am. Physicians* 50: 1156, 1935.
2. Hertz, S., Roberts, A., and Evans, R. D.: Radioactive Iodine as an Indicator in the Study of Thyroid Physiology, *Proc. Soc. Exper. Biol. & Med.* 38: 510, 1938.
3. Hertz, S., Roberts, A., Means, J. H., and Evans, R. D.: Radioactive Iodine as Indicator in Thyroid Physiology; Iodine Correction by Normal and Hyperplastic Thyroids in Rabbits, *Am. J. Physiol.* 128: 565, 1940.
4. Hertz, S., and Roberts, A.: Application of Radioactive Iodine in Therapy of Graves' Disease, *J. Clin. Investigation* 21: 624, 1942.
5. Hamilton, J. G.: Use of Radioactive Tracers in Biology and Medicine, *Radiology* 39: 541, 1942.
6. Hamilton, J. G., and Lawrence, J. H.: Recent Clinical Developments in the Therapeutic Application of Radio-Phosphorus and Radio-iodine, *J. Clin. Investigation* 21: 624, 1942.
7. Rawson, R. W., Hertz, S., and Means, J. H.: Cyanate Goiter in Man: Report of a Case With Histological and Metabolic Studies, *J. Clin. Investigation* 21: 624, 1942.
8. Briard, S. P., McClintock, J. T., and Baldrige, C. W.: Cost of Work in Patients With Hypermetabolism Due to Leukemia and to Exophthalmic Goiter, *Arch. Int. Med.* 56: 30, 1935.

an increase in body weight. The more extensive studies of Williams and Bissell<sup>20</sup> concerned nine patients who were treated with thiouracil. All had had typical manifestations of thyrotoxicosis over periods from six months to twenty-two years. In most instances the thyroid glands were enlarged. Initial basal metabolic rates ranged from plus 36 to plus 88. In all cases the basal had returned to normal with an average of plus 1 for the group within from three to seven weeks following institution of treatment. In four weeks there was a decrease in the protein-bound iodine of the plasma to normal or below. Williams showed also that administration of thiouracil did not interfere with the predicted effect of 1.5 Gm. of desiccated thyroid in two cases of myxedema. His observations confirmed animal experiments which indicated that thiouracil does not interfere with the action of preformed thyroxin.

These preliminary observations showed the remarkable effect of thiouracil on the basal metabolic rate. From both theoretical and practical standpoints it was of great interest to inquire whether the fall in oxidative rate was accompanied by the changes which are ordinarily employed as criteria for good therapeutic results from iodine, radiation, or surgical treatment. The question was pertinent since it is well known that the variations in basal metabolic rate encountered in fever, in leucemia, in Addison's and Fröhlich's diseases, and in dinitrophenol poisoning are not necessarily accompanied by other metabolic and circulatory changes which characterize variations in activity of the thyroid gland. It would not be impossible that the effect of thiouracil on oxidative rate might be accomplished by some mechanism other than by diminishing the amount of circulating thyroid hormone.

Observations made by Sloan and Shorr<sup>21</sup> demonstrated that thiouracil produces changes in circulation rate, pulse rate, blood pressure, calcium and nitrogen balance, creatin metabolism, and cholesterol levels which were qualitatively identical with those achieved by the successful use of iodine, x-ray, or thyroidectomy. The effects of the drug are physiologic in the sense that it tends to correct those functions which are disturbed or exaggerated in thyrotoxicosis.

The effects of thiouracil are now being studied in many clinics. It has been found in the great majority of cases of Graves' disease that freedom from thyrotoxic symptoms may be attained by a few weeks of intensive treatment with thiouracil and that essentially normal conditions may be maintained indefinitely by administration of small amounts of the drug. It has also been shown in a few cases by Astwood<sup>22</sup> that withdrawal of the drug after six to nine months of treatment does not result in recurrence of thyrotoxicosis. Unfortunately, it has also been found that thiouracil possesses toxic properties. Granulocytopenia, early noted by Astwood,<sup>19</sup> has resulted in several deaths, one of which has been reported.<sup>23</sup> Use of the drug has also been followed not infrequently by eruptions<sup>2</sup> and by periods of pyrexia.<sup>24</sup>

## CHEMOTHERAPY IN HYPERTHYROIDISM

E. B. ASTWOOD, M.D., BOSTON, MASS.

*(From the Medical Clinic of the Peter Bent Brigham Hospital and the Departments of Medicine and Pharmacology, Harvard Medical School)*

THERE have been extensive clinical trials of a variety of substances with the aim of controlling states caused by overactivity of the thyroid gland.<sup>1</sup> These have been concerned mainly with attempts to inactivate or to neutralize the circulating thyroid hormone or to suppress its production in the thyroid gland. The proposed agents have been classed as "antithyroid substances," although there was often no clear statement of the mechanism by which they were thought to act. One of the first such substances to receive considerable attention was called "antithyroidin," a preparation made from the serum of thyroidectomized animals. Other agents have included various extracts of human and animal blood and tissues, of the serum or urine of animals which had been treated for long periods with various thyroid hormone preparations, and of the urine of patients with various diseases. A miscellaneous group of organic compounds such as various fats, sugars, and vitamins have also been proposed as having therapeutic value in hyperthyroidism. Among the many inorganic compounds such as salts of the heavy metals and halogens which have been explored, iodine remains as the most widely used therapeutic agent for thyrotoxicosis. None of the other substances has come into general use for, in most cases at least, there was little sound rationale for their introduction as therapeutic agents.

### GOITROGENIC AGENTS

The recent development of chemical compounds effective in inhibiting the synthesis of thyroid hormone dates from studies on the mechanism of action of various goitrogenic agents.

Although it had long been known that various substances would cause thyroid enlargement in animals, the mechanisms involved were not exhaustively investigated. In many instances it was established that the goitrogenic action in question could be prevented by iodine, and the view became current that most of the so-called goitrogenic effects operated through a deficiency in iodine.

Recently there were reported from three laboratories, almost simultaneously, new types of goitrogenic agents. Mackenzie, Mackenzie, and McCollum<sup>2</sup> found that sulfaguanidine when fed to rats for short periods of time induced a marked enlargement and hyperplasia of the thyroid gland, an effect that was not inhibited by iodine. Richter and

Clisby<sup>3</sup> showed that phenylthiourea was goitrogenic and Kennedy, Purves, and Griesbach<sup>4</sup> described in detail the goitrogenic action of rape seed—an effect which Kennedy<sup>3</sup> later attributed to allyl thiourea, a possible constituent of rape seed. Detailed studies on the mechanism by which sulfonamides and thiourea induce thyroid enlargement led to the concept that the goiter is compensatory in nature and that the primary action of such compounds is the inhibition of thyroid hormone synthesis.<sup>6,7</sup> This finding suggested that compounds related to the sulfonamides or thiourea might be useful therapeutic agents and consequently the activity of a large number of such compounds was explored.

It was found that the compounds tested could be divided into three classes: thiourea derivatives, those containing an aminobenzene grouping, and the thiocyanates.<sup>8</sup> The thioureas on the whole were the most active and among these thiouracil had the highest activity. The aminobenzene derivatives included the common sulfonamides of which sulfadiazine was the most active. The thiocyanates were distinct from the other two classes in requiring a diet low in iodine; the goitrogenic action was completely inhibited by added iodide. Furthermore Rawson, Tannheimer, and Peacock<sup>9</sup> have shown that the thiocyanate goiter readily takes up radioactive iodine while the enlarged glands resulting from thiouracil administration do not. The only difference thus far found between the first two groups is one of species difference. The aminobenzene derivatives are without effect when administered to chicks,<sup>6,10</sup> whereas various thiourea derivatives are highly effective in this species.<sup>10,11</sup>

On the basis of these observations some of the early work on goitrogens may offer an explanation. Thus, it is tempting to speculate that the goiter produced in rabbits from the feeding of cabbage described by Chesney, Clawson, and Webster,<sup>12</sup> and by Marine and Baumann,<sup>13</sup> as it was completely prevented by iodide,<sup>14</sup> may have resulted from thiocyanates present in the cabbage acting in the presence of a diet which must have been very low in iodine.

Similarly, Purves<sup>15</sup> has recently shown that the goiter produced in rats by feeding rape seed is partially but not completely inhibited by iodide. This may indicate that there are two types of goitrogens present in rape seed, one a thiocyanate inhibited by iodine and the other a thiourea derivative not inhibited. The finding of Marine and associates<sup>16</sup> that the goiter induced by acetonitrile in rabbits is completely inhibited by iodine might now be interpreted in a similar way. Cyanide is known to be converted to thiocyanate in the body as a means of detoxication and it may have been the thiocyanate formed which was responsible for the effect upon the thyroid gland.

In any case it is apparent that the action of cyanides and thiocyanates is inconstant and, being dependent upon low levels of iodine intake, is difficult to control. Studies on goitrogens are thus more readi-

ly performed on the aminobenzene derivatives or on compounds related to thiourea, preferably the latter, which do not appear to suffer the disadvantage of marked species differences.

#### TREATMENT OF THYROTOXICOSIS

*Thiourea*.—In view of the finding in animals that the formation of thyroid hormone is inhibited by relatively nontoxic compounds it seemed of interest and importance to determine whether the excessive production of hormone in human thyrotoxicosis could be checked by the administration of one of these agents.

The first compound to be tested clinically was thiourea, a compound which appeared to be particularly nontoxic in animals. During the early part of 1942 several normal and two hyperthyroid individuals were given from 1 to 2 Gm. doses of this compound for several days. No toxic effects were noted and there was no immediate change in the metabolic rate. When treatment was continued for several weeks, improvement of thyrotoxic symptoms and a satisfactory response of the basal metabolic rate were observed.<sup>17</sup>

This effect of thiourea was confirmed and extended by the studies of Himsworth,<sup>18</sup> who treated six patients with hyperthyroidism with good results. Thiourea was found to be unpleasant to some persons because of the aftertaste and because of the unpleasant odor that was imparted to the breath. Himsworth found that some of his patients experienced nausea and vomiting. In the first case referred to, treatment had to be discontinued because of the development of a skin rash. This complication is apparently quite common with thiourea as it has subsequently occurred in a number of patients treated with adequate doses. A recent note also records the occurrence of granulocytopenia and thrombocytopenia<sup>19</sup> in a patient treated with thiourea. Although a number of investigators have studied the effects of thiourea in hyperthyroidism and will doubtless publish their results shortly, its activity appears to be too low and the incidence of a toxic reaction too high for it to be recommended as a useful drug.

*Thiouracil*.—Shortly after the first successful trials with thiourea had been initiated, a study of the activity of a number of related compounds revealed that thiouracil was a more highly active substance.<sup>8</sup> Most of the studies to date on the chemotherapy of thyrotoxicosis have been confined to this drug, which on the basis of recent work appears to have an activity approximately ten times that of thiourea on a weight basis; molecule for molecule, thiouracil is thus seventeen times as active as thiourea.

When thiouracil was tested in clinical hyperthyroidism its high activity was soon apparent. A total daily dose of from 0.2 to 0.6 Gm. was found to be effective in controlling the symptoms of hyperthyroidism and in reducing the basal metabolic rate to normal.<sup>17</sup> In one case a dose of 2 Gm. daily resulted in the production of a severe but not

er during treatment. However, accurate estimates of size in such cases are difficult and are complicated by changes in the consistency or firmness of the gland. Under thiouracil treatment the thyroid was noted to become softer, in fact in some cases this made it impossible to determine the borders and outline of the thyroid. In patients with initially small glands this factor would then give the erroneous impression of a decrease in size and in some cases the softness made the gland impalpable. Changes in size were more definite in those exhibiting large diffuse goiter prior to therapy. In most of these there was an unquestionable increase in size during the first few weeks of therapy and an increase in the signs of hyperemia. Later on the gland slowly regressed and in some the thrill and bruit, previously very striking, entirely disappeared. In two cases the addition of a small dose of iodine to the thiouracil treatment seemed to be responsible for a sudden cessation of the bruit and a decrease in the size of the gland. In these two instances the metabolic rate fell precipitously coincident with the giving of iodine, in one it fell from normal to a level of -25 per cent in the course of a few weeks although only a small maintenance dose of thiouracil was being given.

The course of the therapeutic response as just described has been found to be quite uniform in most cases of primary hyperthyroidism. Three patients with typical Graves' disease exhibited a greatly delayed response to thiouracil and the only factor common to each was the prior administration of full doses of iodine. Presumably iodine therapy tends to cause the deposition of large stores of thyroid hormone within the gland; if the current concepts of the manner of action of thiouracil are correct, then these delayed responses become intelligible. As previously suggested,<sup>17</sup> the major portion of the stored hormone must become exhausted before an effect upon the metabolic rate can be achieved. The action of the drug is to block the formation of new hormone and it is without effect on the release or the activity of the hormone stored within the thyroid gland. It has consequently been the recent practice to discontinue iodine, if it has been given, for some weeks prior to starting thiouracil therapy.

Long latent periods have also been noted in several instances of toxic nodular goiter and in these, as in the iodine-treated cases of Graves' disease, there is presumably a large amount of hormone-containing colloid within the gland, and presumably the same mechanism is operative in causing a delayed response. This factor is apparently also responsible for the fact that in persons with normal glands a prolonged period of treatment is required before a fall in the metabolic rate occurs. In the normal individual there is a large store of hormone and the time required for the gland to become depleted is further extended by the fact that the rate of release of hormone is much slower than in the case of the overactive glands of hyperthyroid individuals.

*Remission.*—In the first few treated patients therapy was withdrawn shortly after the metabolic rate had reached normal in order further to establish that the observed effect was attributable to the drug. It was apparent from these tests that all the manifestations of the disease returned promptly when the treatment was discontinued and that no lasting improvement could be obtained from short periods of medication. In subsequent cases the treatment was continued for an arbitrary period of from six to eight months in dosages that maintained a normal or somewhat subnormal metabolic rate. During this period the patients remained free of symptoms and appeared normal in every way with the exceptions of continued eye signs and thyroid enlargement in some cases. At some time during this period of treatment a spontaneous remission presumably occurs but as yet no means has been found to determine when this takes place. Of the twelve patients who have thus far completed such a course of therapy and from whom the drug has been withdrawn, nine have been under close observation for from two to six months. In each case the metabolic rate has remained normal, body weight has been maintained, and no symptoms of hyperthyroidism have appeared.<sup>26</sup> As the effect of the drug could be expected to subside within a few days after the last dose, it must be presumed that remissions occurred. Thus far there is no experimental basis for the assumption that the thiouracil was responsible for the remissions, and it is more reasonable to suppose that the drug merely controlled the disease and maintained a state of health which permitted a spontaneous and apparently complete recovery to occur.

#### DISCUSSION

There remains little doubt that thiouracil and related compounds can effectively and perhaps completely block the synthesis of thyroid hormone. Administered to hyperthyroid patients the value of such drugs as therapeutic agents can scarcely be questioned. Advantages over other forms of therapy include the avoidance of surgical operation, the reproducible nature of the response, the lack of any evidence of the development of tolerance or refractiveness, and ease with which the metabolic rate can be controlled at any desired level.

The main disadvantage of this form of therapy is the occurrence of toxic reactions in a certain small percentage of cases. The use of small doses and further investigations into the nature of the toxic effects may help to reduce the incidence or severity of such reactions. As thiouracil is only one of a number of active compounds it seems quite likely that equally active substances which are productive of fewer reactions may be discovered. Until such new drugs are developed there seems to be no cause to restrict the use of thiouracil in the treatment of thyrotoxicosis. Dangerous toxic reactions are apparently quite rare; the more common reactions may be such that treatment



has to be discontinued but in such instances nothing has been lost. The subsequent response to iodine remains unaffected and surgery can be performed when necessary without added danger.

Another drawback to this treatment involves its possible effect upon the size of the thyroid gland. Individuals with very large goiters may experience a further growth of the gland which could result in symptoms from pressure on adjoining structures. The current practice of removing large goiters for cosmetic reasons or because of pressure symptoms and removing nodular goiters because of the possibility of neoplastic changes is probably sound. The possibility of using thiouracil as a means of preparing such cases for operation is being explored in a number of clinics.

#### SUMMARY

Many substances have from time to time been proposed as remedies for hyperthyroidism, but with the exception of iodine none has been generally accepted.

A brief review of the origin of effective chemotherapeutic agents for thyrotoxicosis and a summary of some of the clinical data thus far available indicate that compounds such as thiouracil are effective in the treatment of this disorder. Serious toxic reactions are rare and the ease with which the disease can be controlled recommends this form of treatment. The frequency of spontaneous remission during therapy indicates that lasting therapeutic effects may be anticipated.

#### REFERENCES

1. Petrova, A. N.: Substances With Antithyroid Action, *Advances in Modern Biol. (U. S. S. R.)* 15: 65, 1942.
2. Mackenzie, J. B., Mackenzie, C. G., and McCollum, E. V.: Effect of Sulfanilylguanidine on the Thyroid of the Rat, *Science* 94: 518, 1941.
3. Richter, C. P., and Clisby, K. H.: Graying of Hair Produced by Ingestion of Phenylthiocarbamide, *Proc. Soc. Exper. Biol. & Med.* 48: 684, 1941.  
Idem: Toxic Effects of Bitter Tasting Phenylthiocarbamide, *Arch. Path.* 33: 46, 1942.
4. Kennedy, T. H., and Purves, H. D.: Studies on Experimental Goitre. I. The Effect of Brassica Seed Diet on Rats, *Brit. J. Exper. Path.* 22: 241, 1941.  
Griesbach, W. E., II: Changes in the Anterior Pituitary of the Rat, Produced by Brassica Seed Diet, *Ibid.* 22: 245, 1941.  
Griesbach, W. E., II, Kennedy, T. H., and Purves, H. D., III: The Effect of Goitrogenic Diet and Hypophysectomized Rats, *Ibid.* 22: 249, 1941.
5. Kennedy, T. H.: Thio-ureas as Goitrogenic Substances, *Nature, London* 150: 233, 1942.
6. Mackenzie, C. G., and Mackenzie, J. B.: Effect of Sulfonamides and Thioureas on the Thyroid Gland and Basal Metabolism, *Endocrinology* 32: 185, 1943.
7. Astwood, E. B., Sullivan, J., Bissell, A., and Tyslowitz, R.: Action of Certain Sulfonamides and of Thiourea on the Function of the Thyroid Gland, *Endocrinology* 32: 210, 1943.
8. Astwood, E. B.: The Chemical Nature of Compounds Which Inhibit the Function of the Thyroid Gland, *J. Pharmacol. & Exper. Therap.* 78: 79, 1943.
9. Rawson, R. W., Tannheimer, J. F., and Peacock, W.: The Uptake of Radioactive Iodine by the Thyroids of Rats Made Goiterous by Potassium Thiocyanate and by Thiouracil, *Endocrinology* 34: 1, 1944.
10. Astwood, E. B., Bissell, A., and Hughes, A. M.: Inhibition of the Endocrine Function of the Chick Thyroid, *Federation Proc.* 3: 2, 1944.

- 11 Mixer, J. P., Reineke, E. P., and Turner, C. W.: Effect of Thiouracil and Thiourea on the Thyroid Gland of the Chick, *Endocrinology* 34: 168, 1944
- 12 Chesney, A. M., Clawson, T. A., and Webster, B.: Endemic Goiter in Rabbits, *Bull. Johns Hopkins Hosp.* 43: 261, 1928
- 13 Marine, D., and Baumann, E. J.: Further Studies on the Etiology of Goiter the Effect of Cyanides, *Tr. A. Am. Physicians* 47: 261, 1932.
- 14 Marine, D.: The Pathogenesis and Prevention of Simple or Endemic Goiter, *J. A. M. A.* 104: 2334, 1935
- 15 Purves, H. D.: Studies on Experimental Goiter. IV. The Effect of Diiodo tyrosine and Thyroxine on the Goitrogenic Action of Brassica Seeds, *Brit. J. Exper. Path.* 24: 171, 1943
- 16 Marine, D., Baumann, E. J., Spence, A. W., and Cipra, A.: Further Studies on the Etiology of Goiter With Particular Reference to the Action of Cyanides, *Proc. Soc. Exper. Biol. & Med.* 29: 772, 1932
- 17 Astwood, E. B.: Treatment of Hyperthyroidism With Thiourea and Thiouracil, *J. A. M. A.* 122: 78, 1943
- 18 Hamsworth, H. P.: Thyrotoxicosis Treated With Thiourea, *Lancet* 2: 465, 1943
- 19 Newcomb, P. B., and Deane, E. W.: Thiourea Causing Granulopemia and Thrombopenia, *Lancet* 246: 179, 1944
- 20 Williams, R. H., and Bissell, G. W.: Thiouracil in the Treatment of Thyrotoxicosis, *New England J. Med.* 229: 97, 1943; *Science* 98: 156, 1943
- 21 Palmer, V.: Hyperthyroidism and Thiouracil, *Bull. School Med. Univ. Maryland* 28: 125, 1944
- 22 Gabrilove, J. L., and Keit, M. J.: Sensitivity to Thiouracil, *J. A. M. A.* 124: 504, 1944
- 23 Welshman, B. C.: Effect of Thiouracil on White Cells, *Lancet* 246: 195, 1944
- 24 Rawson, R. W., Evans, R. D., Means, J. H., Peacock, W. C., Lerman, J., and Cortell, R. E.: The Action of Thiouracil Upon the Thyroid Gland in Graves' Disease, *J. Clin. Endocrinol.* 4: 1, 1944
- 25 Astwood, E. B.: Medical Treatment of Hyperthyroidism, *Bull. New England M. Center* 6: 1, 1944
- 26 Astwood, E. B.: Control of Hyperthyroidism With Thiouracil and Continued Remission After Therapy, *J. Clin. Investigation* 23: 1944
27. Astwood, E. B.: Thiouracil Treatment in Hyperthyroidism, *J. Clin. Endocrinol.* 4: 229, 1944.

## FACTORS INFLUENCING OPERABILITY AND MORTALITY RATE IN GOITER

WARREN H. COLE, M.D., CHICAGO, ILL.

(From the Department of Surgery, University of Illinois, College of Medicine, and the Illinois Research and Educational Hospital.)

AS IN most other surgical diseases, the results in the mortality rate following operation for goiter have improved considerably during the past one or two decades, but due to factors primarily not related to surgical technique. Surgical technique in thyroidectomy itself has changed or improved but little during the past three or four decades. However, numerous improvements in preoperative preparation (for example, use of thiouracil), choice of patients for operation, etc., have been made during this period. Most of these improvements are related directly to a better understanding and fuller appreciation of physiologic principles. Most of the physiologic principles are new. However, some are old and very obvious: it is amazing that so little attention has been paid to them during the years past.

### PREOPERATIVE PREPARATION

Since the mortality rate of thyroidectomies in patients with mildly toxic goiter is very low indeed, the adherence to strict principles in preoperative treatment becomes much less important than it is in patients with severe toxicity. In other words, patients with mildly toxic goiter may require very little preoperative preparation. As will be discussed later, factors other than preoperative preparation must be considered seriously in patients with severely toxic goiter.

*Administration of Iodine or Thiouracil.*—Unquestionably, the administration of iodine or thiouracil in the preparation of patients for operation for toxic goiter is the greatest single factor in the maintenance of low mortality rate. The profession owes a debt of gratitude to Plummer for rediscovering the influence of iodine in toxic goiter and to Astwood for the clinical demonstration of the beneficial effects of thiouracil.

The dose of iodine usually given is from 5 to 15 minims three times daily, although a smaller dose is probably adequate. Doses larger than this are highly undesirable since nausea may be produced by an excessive dose of iodine. This would therefore defeat one of the primary purposes in the preparation of the patient, namely, to improve his nutrition. The greatest error in iodine therapy is continued use of the drug over a long period, that is, beyond preoperative preparation. The next greatest error lies in the assumption held by many physicians that

maximum benefit of iodine therapy is attained between the tenth and fourteenth day. It is true that the average patient with thyrotoxicosis achieves sufficient beneficial effect at the end of fourteen days to be a perfectly safe operative risk. However, in patients who are extremely toxic, the optimum state of operability is practically never achieved within this period. In other words, the physician must maintain iodine therapy for many more days, realizing that improvement will still be achieved and that operations can be performed much more safely at a later date. The author admits the possibility of the patient becoming iodine-fast but wishes to emphasize that this danger is not as important as many clinicians would lead one to believe. It should be emphasized that these remarks on the use of iodine now apply only to those few patients who are sensitive to thiouracil or do not respond to it. However, some clinicians are using iodine and thiouracil together in pre-operative preparation of the patient, giving thiouracil for a few weeks before iodine therapy is started.

The administration of thiouracil as introduced clinically by Astwood,<sup>1</sup> and discussed elsewhere in this symposium, may eliminate most of the worry on the part of the clinician in treating patients with a severe grade of toxicity. Although the effect of thiouracil requires a longer period of treatment than noted in iodine therapy, the decrease in toxicity is much more pronounced. In other words, the danger of a postoperative crisis and other complications arising from severe toxicity may be eliminated entirely with thiouracil. The fact that it requires a much longer time than iodine for its beneficial effect may prevent its routine adoption in patients with mildly toxic goiter. On the contrary, use of iodine in patients with severely toxic goiter may become obsolete except to supplement thiouracil. As discussed elsewhere in this symposium, continued use of thiouracil may result in permanent cure in many cases without the aid of operative therapy.

*Increased Caloric Intake.*—Although the factors in the pathogenesis of toxicity in patients with thyrotoxicosis are poorly understood, it is nevertheless surprising what little microscopic evidence of damage from excess production of thyroxin or allied compounds is found. It is, of course, well known that the increase in output of thyroid hormone (or abnormal chemical related to it) is largely responsible for the tachycardia and cardiac damage. Nevertheless, a great portion of the manifestations and pathologic changes are related to the negative caloric balance, largely secondary to the increased metabolism. It is, therefore, obvious that restoration of nutritional balance is exceedingly important, particularly in preparation of the patient for operation. The importance of this disturbance can be appreciated more readily when we realize how much greater than normal is the metabolic activity in toxic goiter. The increase in the metabolic rate may be sufficient to burn more than two or three times the amount of calories consumed by the average individual. It therefore becomes obvious that the cal-

oric intake must be increased accordingly before the patient can show an improvement in his nutritional status.

We place every patient with thyrotoxicosis of more than average degree on a diet of 5,000 calories per day. Men who are extremely toxic will frequently eat as much as 6,000 calories per day. As a matter of fact, caloric intake should be increased as long as the patient is capable of consuming additional food. Occasionally, in these severely toxic patients, administration of even this much food will not produce an appreciable gain in weight. Under such circumstances it may be wise to supplement the oral intake by intravenous glucose and amino acids (Elman<sup>2</sup>), at least over a period of a few days in order to achieve operability. The necessity of supplementing oral intake with intravenous solutions will be encountered most dramatically in the patients who are admitted in crisis or precrisis state. However, very frequently certain patients (particularly women) will have poor appetites, and be unable to eat a sufficient quantity of food even though they are not toxic enough to be classified as in a precrisis state.

*Conservation of Energy.*—Since a patient with toxic goiter is burning up food at a much greater rate than a normal individual, it becomes obvious that energy must be conserved at all possible points. Obviously the patient must be removed from manual labor or any activity which requires undue muscular exertion. However, he must not be confined to absolute bed rest since that produces a severe degree of muscle atrophy even within a short period of a few days. The patient should, therefore, be allowed to be up and about, so that he obtains sufficient exercise to prevent muscle atrophy. However, patients who are in a state of cardiac decompensation, and patients who are in crises or impending crises, represent exceptions and must be confined to absolute bed rest until these states are corrected.

Since sleep is so important in the conservation of energy, the patient must be urged to spend eight or nine hours in bed at night and take an afternoon nap two or three hours daily as part of the preoperative treatment. Since one of the manifestations of thyrotoxicosis is sleeplessness, the patient with severe toxicity will invariably need help in obtaining sufficient sleep. With few exceptions the routine administration of one of the less harmful sedatives, such as phenobarbital and allied compounds, will be indicated. It may be sufficient to limit the drug to a dose in the evening on retiring, although there is no objection to giving the drug two or three times daily to patients who are severely toxic.

*Reduction of Psychic Trauma.*—Unquestionably, excitement and worry increase the manifestations of thyrotoxicosis and therefore should be reduced to an absolute minimum, particularly if the patient is already toxic. Sources of excitement and worry are, of course, innumerable and include such factors as illness in the family, too much

social activity, financial difficulties, family incompatibility, and unruly children. Under such circumstances it will be necessary to remove the patient from family surroundings and take him to the hospital. Members of the family should be instructed not to inform the patient of family troubles or other difficulties which might increase worry. In the author's opinion, the severely toxic patient must be removed to a hospital for preoperative preparation, but the patient with mild toxicity should be ambulatory during preoperative care. In our clinic, at least three-fourths of the patients are prepared for operation in the outpatient department and are brought into the hospital two or three days before operation, for confirmation of operability.

*Treatment of Complicating Diseases.*—It is, of course, essential that the patient be examined thoroughly, so that no complicating diseases are overlooked. Diseases such as cardiac decompensation will, of course, be recognized at once since the major symptoms will be related to this condition. On the contrary, certain serious diseases, such as diabetes, may be discovered only upon thorough examination including laboratory work. Studies made by Regan and Wilder<sup>3</sup> revealed an incidence of diabetes in 1.7 per cent of patients with toxic diffuse goiter, which was identical to the incidence among all types of patients applying at the Mayo Clinic for medical care. However, in toxic nodular goiter the incidence of diabetes was much greater, being encountered in 5.6 per cent of the patients.

Hepatic insufficiency (as emphasized by McIver<sup>4</sup> and others) in a mild form is common; now and then it is the primary cause of a postoperative death. Such conditions must be recognized and treated before operation. Some of these conditions are entirely unrelated to the thyrotoxicosis whereas others are secondary to thyrotoxicosis. Details of the treatment of these conditions are discussed elsewhere in this symposium.

*Miscellaneous Therapy.*—In the author's opinion x-ray treatment may be very beneficial in the preoperative preparation in severely toxic patients, but is obviously indicated only in that small group of severely toxic patients who do not respond to thiouracil or iodine or both. There is no truth in the statements offered by some surgeons that x-ray treatment adds tremendously to operative difficulties. Very few, if any, adhesions are produced by x-ray therapy. It is true that the firmness of the gland may be increased but this will usually be an advantage to the surgeon since friability frequently leads to an increase in hemorrhage incident to the operation. True enough, the maximum effect of x-ray therapy may not be attained in less than four to six weeks. However, except during the two or three days following treatment itself, there should be no deleterious effects from radiation of the gland.

As an example of the value and danger of x-ray therapy, I would like to summarize briefly our experience (before thiouracil was available) with one of the most toxic patients we have had. This individual, a woman

about 30 years of age, entered the hospital in a precrisis state and after weeks of intensive therapy was still obviously inoperable. X-ray therapy was decided upon and was instituted. A day or two following radiation, which was given over a period of a few days, she developed a severe increase in symptoms and was in a state of mild crisis. During this period she became jaundiced, indicating an increase in hepatic insufficiency. For a time it appeared that the institution of radiation may have been an error. However, during the course of the next few weeks she showed gradual improvement and for the first time since admission, many weeks previously, began to show a gain in weight. For the five weeks following radiation she improved to such an extent that she was considered operable according to the prerequisites described later. The patient was submitted to operation, consisting of removal of only one lobe. This was tolerated well and the second lobe was removed three or four weeks later.

Curtis and associates<sup>5</sup> have demonstrated a negative calcium balance in hyperthyroidism, thereby illustrating the need for calcium therapy. In addition, it is agreed that certain vitamins, particularly B<sub>1</sub>, are utilized in a more rapid rate in thyrotoxicosis. Administration of additional vitamin B<sub>1</sub>, therefore, is indicated.

Although every surgeon probably has a scheme of his own for determining operability, everyone will probably agree that the methods of determination of operability are quite arbitrary and therefore subject to many errors. The lack of specificity in outlining methods of determining operability is brought to light more emphatically when one tries to explain to students how a decision regarding operability is arrived at. Under the circumstances it is obvious that if a system utilizing mathematical relationships could be adopted in this determination of operability, the method would be more accurately utilizable by everyone, particularly the students.

#### PREREQUISITES FOR BILATERAL THYROIDECTOMY

It is because of the difficulty in explaining verbally the various physical characteristics required that we have adopted the following group of prerequisites for determining operability. In other words, we require that the patient fit the prerequisites as listed, before he is acceptable for a bilateral thyroidectomy. As will be discussed later, if the patient's condition does not meet the requirements listed here, even after many weeks of therapy, the operation should be done in two stages, removing one lobe at each operation. If the patient's condition fails by a wide margin to meet prerequisites, even lobectomy may be unsafe. As stated previously, the use of thiouracil will eliminate most of this difficulty by eliminating the severe toxicity. However, the occasional instance of sensitivity, or failure of response to the drug, will make it necessary that we retain our knowledge of determination of operability in the presence of severe toxicity.

1. *Gain in Weight.*—Without question the most important requisite for operability in the really toxic patient is gain in weight. *At no time should the severely toxic patient be submitted to thyroidectomy when he has failed to show a weight gain.* As already stated, it is important to start the severely toxic patient on a caloric intake equal to, or more than, 5,000 calories per day. It is not enough to tell the patient to "eat a lot" since that is not sufficiently specific. If he is severely toxic he should be prepared in the hospital for operation. It is difficult in the home to be certain that the patient is getting the 5,000 or 6,000 calorie diet necessary for him. There is no rule as to the exact amount of weight gain necessary. However, certain general premises can be established. For example, if the patient has lost thirty or forty pounds and is obviously malnourished, he will need to gain at least ten to twenty pounds before his physical condition is optimum. On the contrary, if he has lost only eight or ten pounds, a gain of two to four pounds may be adequate to assure the added caloric requirements with replenishment of the various food depots.

*Gain in strength* is allied to a gain in weight and should be considered in the prerequisites. Numerous methods of determining gain in strength are utilized by various clinicians. For example, some surgeons feel that a patient should be strong enough to walk up a certain number of stairs before operation is considered safe. Others say that he should be able to walk from one to two blocks without undue fatigue. Still others have less strenuous muscular feats, such as stepping up on a chair, or lifting weights, as prerequisites. The patient's ability to hold his breath has been suggested as a mechanism for determining operability.

2. *Resting Pulse Rate Should Be Below 110.*—Except in the presence of severe cardiac damage, particularly auricular fibrillation, the pulse rate will be a fairly good index of toxicity. Obviously, the pulse rate will vary throughout the day, depending upon exercise, excitement, etc. We have adopted the principle that the resting pulse rate should be below 110. If a tachycardia of 130 or above develops with only slight excitement or exercise, it is considered that the patient's toxicity is greater, and the cardiac reserve lower than other signs may indicate.

3. *Basal Metabolic Rate Should Be Less Than 50 Per Cent Above Normal.*—Although we appreciate the fact that the basal metabolic rate is subject to considerable error in determining the patient's toxicity, we have nevertheless found it of value when this information is added to the other available data. With few exceptions any patient with a basal metabolic rate of over 50 (after iodine or thiouracil therapy) is apt to have considerable reaction following an operation. The metabolic rate before iodine therapy is of little consequence in determining the operability.



4. *Response to Iodine or Thiouracil Therapy.*—Very rarely indeed will a toxic patient fail to improve markedly under iodine therapy. There should be a definite decrease in intensity of most of the symptoms such as nervousness, excess sweating, sleeplessness, and weakness. Inclusion of this prerequisite is perhaps of more value in establishing the diagnosis in doubtful cases than it is in determining operability, largely because the other prerequisites mentioned are dependent upon a response to iodine or thiouracil.

5. *No Untreated Complications.*—The necessity of effectively treating cardiac decompensation, which is usually secondary to the thyrotoxicosis, is well known and is discussed elsewhere in this symposium. The vital capacity should always be determined in patients with cardiac complications; a figure significantly below normal would suggest that the decompensation was as yet inadequately treated. It must be emphasized that numerous complications unrelated to the thyroid disease may be present. Diabetes, local infections, etc., are representative of unrelated disease which must be treated adequately before operation can be considered.

#### FACTORS RESPONSIBLE FOR INCREASED MORTALITY RATE

Before discussing the numerous factors which might be responsible for an increase in mortality rate, I would like to discuss the various causes of death in our series following thyroidectomy, and indicate the types of goiter in which such disasters might be expected. Obviously, before the time of iodine or thiouracil therapy, development of crisis was the most common cause of postoperative death. Since the use of these drugs, crisis is becoming rare as the cause of death. In fact it might be said that death from crisis following thyroidectomy is inexcusable, and in reality can be prevented with practically no exceptions.

In Table I, it will be noted that in a total of 936 thyroidectomies for toxic diffuse goiter, toxic nodular goiter, and nontoxic nodular goiter, the overall mortality rate was 1.06 per cent. This does not compare too favorably with a rate of 0.76 per cent in 19,700 thyroid operations reported by Lahey.<sup>6</sup> However, it should be added that the rate reported by Lahey represents about the lowest record for a large series. In Table I it will likewise be noted that the mortality rate in the patients with toxic diffuse goiter is lower than in patients with nontoxic nod-

TABLE I  
TYPES OF GOITER AND MORTALITY, 1936 TO 1944  
(Excluding Carcinoma and Woody Thyroiditis)

TYPE	OPERATIONS	DEATHS	MORTALITY (PER CENT)
Toxic diffuse	403	3	0.74
Toxic nodular	297	5	1.6
Nontoxic nodular	236	2	0.85
Total	936	10	1.06

ular goiter. This in reality is not surprising, since we realize that patients having toxic diffuse goiter are relatively young and that preparation is usually carefully carried out before operation is performed. On the contrary, our patients with nontoxic nodular goiter are much older than those with toxic diffuse goiter; even though they are not affected with thyrotoxicosis, they still are subject to serious organic disease, particularly that related to the heart.

Table II reveals that the two deaths encountered in nontoxic nodular goiter were caused by acute heart failure. With the exception of acute heart failure, there is surprisingly little duplication of causes of death in the entire list. For example, the five patients who died following thyroidectomy for toxic nodular goiter, died of a different complication, namely, crisis, hemorrhage, gas gangrene of the buttocks, acute heart failure, and severe glucose reaction.

It is true that the patient listed as having died following the severe glucose reaction might have survived if she had not had a toxic goiter, yet from the clinical findings, there is sufficient reason to believe that she would have survived quite satisfactorily if the severe glucose reaction had not developed. In other words, some of the causes listed are in reality contributory, but are considered to be the most important cause of death. In the entire group of ten deaths, it is obvious that at least four should be classified as preventable, namely, those due to hemorrhage, crisis, and glucose reaction. We, therefore, accept full responsibility for these fatalities, and in retrospect feel that we should have prevented them.

TABLE II  
CAUSES OF DEATH FOLLOWING THYROIDECTOMY

Toxic diffuse	3	<div> 1 Tetany  1 Crisis  1 Acute hepatic insufficiency </div>
Toxic nodular	5	<div> 1 Crisis  1 Hemorrhage  1 Gas gangrene of buttock  1 Acute heart failure  1 Severe glucose reaction </div>
Nontoxic nodular	2	2 Acute heart failure

It is obvious then from the variety of the causes of death shown in our series, that lowering the mortality rate may be difficult, except in the instances such as the four just mentioned. In spite of the great variety of causes of death, the author is convinced that if the mortality rate following operation is much above 1 per cent, insufficient attention is being paid to certain prerequisites, or postoperative care is not what it should be.

Although in a consideration of mortality rates throughout the country the relative incidence of the types of goiter encountered might be

considered as playing a prominent role in the fatalities, I doubt that this factor plays a significant role. The patients in the series herein reported came from Chicago or environs, which is in the center of one of the most prominent goiter belts in the United States. Yet the ratio of toxic diffuse to toxic nodular and nontoxic nodular goiter is almost identical to the ratio reported by Lahey<sup>6</sup> as being encountered in Boston, namely, 2 to 1 to 1, respectively. In our experience, thyroidectomy in patients with toxic nodular goiter is associated with a much higher mortality rate than in toxic diffuse goiter (see Table I). Our death rate was more than twice as high in toxic nodular goiter as in toxic diffuse goiter. I believe that this trend would be maintained in almost all localities although there might be an exception in a series composed largely of private patients, since this group of patients with toxic nodular goiter would be much less likely to postpone treatment of the insidious manifestations so typical of this type of goiter; the symptoms of toxic diffuse goiter are so prominent that charity and private patient alike will come early for treatment before serious organic changes take place.

1. *Inadequate Preparation.*—Unquestionably the most common factor in inadequate preparation is failure on the part of the physician to supply enough food to produce a gain in weight and put the patient on a positive caloric balance.

2. *Wrong Choice of Time for Operation.*—It is well known that the degree of toxicity fluctuates considerably in patients with toxic goiter. Therefore, in the treatment of severely toxic patients it is usually necessary to choose a time for operation when the patient is in a so-called remission. During this time his manifestations may fit into the prerequisites previously outlined although it may require several weeks of therapy before this state of operability can be achieved. It should be remembered that certain features in the daily life of the patient may actually alter the operability. For example, if a patient is confronted with the news of the death of a member of his family, he may immediately revert from a state of operability to one of inoperability, and require several days of therapy before operability is regained.

3. *Lack of Appreciation of the Danger of Complications.*—It need not be emphasized that a patient who has a complication along with hyperthyroidism will, of course, not be as good a risk as a patient without complications. The report of Pemberton and Miller,<sup>7</sup> who note that 81 per cent of their deaths were in thyrocardiac patients, illustrates this point very emphatically. It is obvious that in the group of patients with complications the prerequisites outlined must be met more completely than in other patients.

4. *Errors on the Operating Table.*—Failure to recognize signs of excessive toxicity is probably the most common error made while the

patient is on the operating table. Ordinarily the surgeon has ample warning at this time of the presence of severe toxicity. In the first place, the pulse rate during the anesthesia is an important indication of toxicity. We utilize the principle that if the pulse rate cannot be brought down under 140 with anesthesia, operation is so unsafe that the incision should not even be made; under such circumstances it is advisable to send the patient back for a few more days of treatment. Likewise, if after the removal of one lobe, the patient's pulse starts to rise above 135 or 140, it is usually wise to terminate the operation at this point. The use of an excessive amount of oxygen is likewise an indication of toxicity. If the anesthetist informs the surgeon that it is extremely difficult to keep the patient oxygenated under general anesthesia, it is safe to assume that the patient is probably more toxic than was originally considered. Utilizing the principle just discussed, we have sent many patients back from the operating room before making the incision, and in about 5 per cent of the cases we do the operation in stages, removing the right lobe at the first operation and the left lobe from three to six weeks later. Too frequently the surgeon inflicts too great an operative load upon the patient. The author agrees wholeheartedly with Lahey,<sup>6</sup> who states that many of the deaths encountered are explained on the basis that too much work has been done, namely, that two lobes were removed instead of one. It should be emphasized that if before operation the surgeon has arrived at the decision to do the operation in two stages, rarely is it safe to allow a smooth course on the operating table to change his decision to that of removal of both lobes.

Errors in technique are of less importance in the mortality rate than are errors in judgment. However, if a bilateral recurrent nerve injury is sustained in a severely toxic patient, the excess load of anoxia, tracheotomy, etc., may be sufficient to cause death. On certain occasions, slowness in performance of the operation may be a most important contributory factor in the patient's death. This would be true only in the patient who is severely toxic. Although the author agrees that thyroidectomy should be done with the utmost dispatch in severely toxic patients, he would like to emphasize that efforts to hurry and shorten the operating time have probably done more harm than good, except in emergency circumstances. In general, if a high mortality rate is secondary to inexperience on the part of the surgeon, failure to utilize proper judgment in preoperative care, choosing the proper time for operation, etc., will reflect much more directly on mortality rate than will poor operative technique.

The choice of anesthesia may likewise reflect somewhat in the mortality rate. Perhaps the best example of this might be the use of cyclopropane in a patient with auricular fibrillation who has considerable myocardial damage. Likewise the use of nitrous oxide in the

hands of a poor anesthetist might be dangerous in severely toxic patients, although we realize that experts can handle this agent very well.

5. *Insufficient Vigil in Postoperative Care.*—Perhaps the most common example of fatality resulting from failure to exercise proper postoperative care is failure to recognize and promptly treat postoperative hemorrhage and bilateral injury to the recurrent nerve. Insufficient fluid, too little or too much sedation, failure to utilize oxygen therapy when indicated, and numerous other errors may contribute to a postoperative fatality. Details of these features in postoperative care are discussed at length, elsewhere in this symposium.

#### SUMMARY

The marked improvement in mortality rate following thyroidectomy during the past one or two decades has been due primarily to improvements in our knowledge and application of physiologic principles, particularly as related to preoperative and postoperative care. Preoperative preparation is exceedingly important in patients with severely toxic goiter. The major factors in this preparation of the patient include: (1) administration of iodine or thiouracil; (2) increased caloric intake; (3) conservation of energy; (4) reduction of psychic trauma; (5) treatment of complicating disease; and (6) miscellaneous therapy. Appreciating that the mortality rate is so dependent upon preoperative treatment, we have adopted in our clinic certain prerequisites to be met before a patient is considered safe for bilateral thyroidectomy. These prerequisites are: (1) gain in weight; (2) resting pulse rate below 110; (3) basal metabolic rate below 50; (4) response to iodine or thiouracil; (5) no untreated complications. Of this group of prerequisites, gain in weight is the most important. It is an unforgivable error to subject a patient with severe toxic goiter to bilateral thyroidectomy, unless he has shown a weight gain.

Thiouracil gives promise of revolutionizing our methods of preoperative care and may make operation unnecessary in many patients. However, it is doubtful if the mortality rate may be appreciably lowered in the clinics reporting the best results, largely because relatively few of the deaths encountered in such series of patients will be related to thyrotoxicosis itself. The mortality rate in our series of 936 thyroidectomies was 1.06 per cent. It was lower in toxic diffuse goiter than in either of the two types of nodular goiter. Although almost one-half of our deaths must be considered in the preventable class, the causes were extremely variable. Three patients died of acute heart failure, and two died in crisis. There was no duplication in the other causes of death. A study of factors (other than coincidence) which might be responsible for a lethal outcome includes: (1) inadequate preparation; (2) wrong choice of time for operation; (3) lack of appreciation of the dangers of complications; (4) errors on the operating table; (5) insufficient vigil in the postoperative care.

It should be emphasized again that many of the precautions described here will be of only slight importance in the great majority of patients who respond to thiouracil. However, since an occasional patient will be sensitive to the drug or will not respond to it, information gained about severely toxic patients through many years' experience with them should not be cast aside.

#### REFERENCES

1. Astwood, E. B.: Treatment of Hyperthyroidism With Thiourea and Thiouracil, *J. A. M. A.* 122 78, 1943.
2. Elman, Robert: Parenteral Replacement of Protein With the Amino Acids of Hydrolyzed Casein, *Ann. Surg.* 112: 594, 1940.
3. Regan, J. F., and Wilder, R. M.: Hyperthyroidism and Diabetes, *Tr. Am. A. Study Goiter*, p. 113, 1940.
4. McIver, M. E.: Liver Changes in Hyperthyroidism, *SURGERY* 12: 654, 1942.
5. Puppel, I. D., Klassen, K. P., and Curtis, G.: Calcium Metabolism in Thyroid Disease, *Tr. Am. A. Study Goiter*, p. 221, 1939.
6. Lahey, Frank: Aids in Avoiding Serious Complications in Thyroidectomy, *Ann. Surg.* 113: 730, 1941.
7. Pemberton, J. deJ., and Miller, J. M.: Surgery for Thyroid Disease Associated With Cardiac Disease, *Tr. Am. A. Study Goiter*, p. 32, 1940.

## ANESTHESIA IN THYROID SURGERY

R. CHARLES ADAMS, M.D.,\* AND CLAUDE F. DIXON, M.D.†  
ROCHESTER, MINN.

**M**ETHODS of anesthesia for operations on the thyroid gland are many and diversified and the approach to the anesthetic problems involved in this type of surgery is governed somewhat by the conditions under which the surgeon likes to work. Of the available methods from which to choose, most provide satisfactory working conditions for the surgeon and an adequate margin of safety for the patient.

Surgeons performing thyroid operations may be divided roughly into two groups from the standpoint of their choice of anesthesia. Surgeons of one group prefer that their patient be asleep throughout the course of the operation and hence favor inhalation or intravenous anesthesia. Those of the other group favor having the patient awake, at least intermittently, throughout the operation in order that his speaking voice may be checked at intervals for possible damage to the recurrent laryngeal nerve and to permit straining in order that all potential bleeding vessels may be ligated securely before the wound is closed. This group prefers local or regional anesthesia with only the intermittent use of a general anesthetic agent.

Thyroid surgery presents certain anesthetic problems related both to the nature of the disease and to the site of the operation that are not encountered in most other types of surgery. Despite the fact that a surgeon may prefer a certain type of anesthesia in uncomplicated cases, some conditions make certain types of anesthesia preferable to others. Such conditions might include very large glands; substernal goiters; those which are causing undue pressure on, or displacement of, the trachea; dyspnea; cardiac disease; and severe thyrotoxicosis. In this type of case the anesthetic management is of greater importance than for an operation for a simple nontoxic adenomatous goiter.

Some features of the anesthetic management of thyroid patients bear particular attention. The fact that many patients suffering from goiter have varying degrees of elevation of emotional tone necessitates individualized adjustment of the preliminary medication to effect adequate preanesthetic sedation. Since the site of the operation is in close proximity to the trachea and upper respiratory passages, respiratory obstruction is always a potential hazard. Because of the elevation of the metabolic rate, anoxemia is not only undesirable but even dangerous, since these patients have a high oxygen requirement.

\*Section on Anesthesia, Mayo Clinic.

†Division of Surgery, Mayo Clinic.

Received for publication, March 25, 1944.

Respiratory obstruction, in addition to inhibition of oxygenation, complicates the surgical procedure by increasing bleeding in the operative field. These are some of the considerations that must be weighed in selecting the anesthetic agent for the patient suffering from a disease of the thyroid.

#### PRELIMINARY MEDICATION

Patients who have a disease of the thyroid, particularly those who have severe hyperthyroidism, require adequate preliminary sedation in order to lower their emotional tone to somewhere near basal level. Various premedicants and basal sedatives have been employed for this purpose. Avertin with amylene hydrate has attained favor with many surgeons for the production of basal anesthesia in operations on the thyroid. We prefer the use of morphine and a barbiturate in divided doses since this method appears to have greater flexibility than the single administration of basal sedatives by rectum. Pentobarbital sodium is administered the night before operation in doses of  $1\frac{1}{2}$  to 3 gr. (0.1 to 0.2 Gm.). The dose should be sufficient to insure a good night's rest. On the morning of the operation the dose or doses of pentobarbital sodium are repeated and  $\frac{1}{6}$  gr. (0.01 Gm.) of morphine and  $\frac{1}{450}$  gr. (0.00043 Gm.) of atrophine are administered hypodermically at least one-half hour before the time of operation. The important feature is to adjust the dosage and timing of the premedicants so that the patient reaches the operating room in a drowsy and peaceful state of mind. Some physicians prefer to have the patient asleep before leaving his room.

In spite of a carefully planned course of preliminary medication, such things as unforeseen delays result in many patients reaching the operating room inadequately premedicated. When this occurs, additional doses of pentobarbital sodium may be administered intravenously after the patient reaches the operating room. The drug, in 2.5 per cent solution, is injected slowly and intermittently until the basic level of sedation is reached. This should render the patient drowsy but not asleep. If the thyroid condition has resulted in any degree of respiratory obstruction, only minimal sedation is indicated in order to avoid respiratory depression, obstruction, and anoxemia.

Much stress has been placed on the preoperative management of the patient suffering from disease of the thyroid in regard to absolute rest and quiet and shielding him from the knowledge of anything relative to the operation or its time. No doubt such measures are justified in the management of patients who are extremely hyperactive but for the average patient we feel that these precautions are unnecessary, provided the course of preliminary medication is adequate. Most of these patients get along well on ordinary routine preoperative management and it often seems that special attentions render them more, instead of less, apprehensive.



## ANESTHETIC AGENTS AND METHODS

When the thyroid condition has resulted in severe metabolic imbalance and hyperfunction, anesthetic agents having the least toxicity and which interfere least with metabolic function are indicated.

*Local and Regional Anesthesia.*—Provided the patient has been well premedicated, local anesthesia has many advantages. It is adequate for most stages of the operation and produces the minimum of secondary toxic effects. Our method consists in blocking the superficial cervical plexus bilaterally with 1 per cent solution of procaine hydrochloride or metycaine and infiltrating the region of incision with a 0.5 per cent solution of one of these drugs. The use of epinephrine as a vasoconstrictor in the local anesthetic solution is contraindicated if the gland is of the toxic or exophthalmic type. It is to be remembered that some patients are definitely sensitive to epinephrine and many so-called procaine reactions have been due to this vasoconstrictor. In cases of nontoxic thyroid conditions, cobefrin may be used as a vasoconstrictor. Usually, sufficient duration of anesthesia is obtained without a vasoconstrictor, particularly if metycaine is used. Most of the discomfort under local anesthesia occurs when the lobes are being delivered and when traction is made on the gland. Brief periods of supplementation with nitrous oxide and oxygen at these times render the patient comfortable. The local anesthesia permits the use of sufficient oxygen with the nitrous oxide to prevent most patients from becoming cyanotic. This combination of methods makes it possible to have the patient awake whenever necessary. The advantages of this have been mentioned heretofore.

*Block Anesthesia.*—In certain cases in which the patient is an extremely poor risk, because of debility, toxicity, or the size and position of the gland, it may be undesirable to put the patient to sleep. In such cases complete cervical block will provide anesthesia of all the deep and superficial structures. This is accomplished by bilateral injection of 1 per cent solution of procaine or metycaine into the second, third, and fourth cervical nerves and the superficial cervical plexus. The region of operation is also infiltrated with a 0.5 per cent solution of one of the agents.

*Inhalation and Intratracheal Anesthesia.*—Nitrous oxide, ethylene, and cyclopropane have all been employed in thyroid surgery and, because of their inert nature, are suitable agents. However, nitrous oxide-oxygen anesthesia alone often fails to provide sufficient depth of anesthesia without the patient becoming cyanotic, which is to be avoided. To a lesser degree this also applies to ethylene. The value of these agents in thyroid surgery is enhanced if they are complemented by local or regional anesthesia.

Cyclopropane is considered by many to be the agent of choice if inhalation anesthesia is to be used. It produces quiet breathing, while

anesthesia can be maintained with a comparatively high concentration of oxygen. These features together with the rapid recovery period commend its use in operations on goiter. The main drawback of cyclopropane is its explosibility but this need not necessarily contraindicate its use if proper precautions are observed. With the proximity of the field of operation to the upper respiratory passages, the employment of electrical apparatus during the operation would, we feel, contraindicate its use.

Most surgeons and anesthetists agree that as a rule ether is not a desirable agent for routine use in operations on the thyroid. However, if it is felt that an inhalation anesthetic agent is indicated (perhaps with an intratracheal tube) moderate amounts of ether may be administered with comparative safety to a patient for whom a gaseous anesthetic agent is inadequate. For a child undergoing an operation on the thyroid, inhalation anesthesia, preferably intratracheal, becomes the method of choice and moderate amounts of ether may be administered without untoward effect.

If an inhalation anesthetic agent is preferred by a surgeon, the operation may be performed with greater facility if an intratracheal tube is used. Its use will permit a continuously free airway, regardless of the position of the patient's head or pressure or traction exerted on the larynx and trachea. In addition, adequate ventilation and oxygenation may be maintained. Intratracheal anesthesia is probably the method resulting in the most efficient second-to-second control if the gland is large or substernal or if there is pressure on, or deviation of, the trachea. It is good prophylaxis to have an intratracheal tray in readiness, with several sizes of intratracheal tubes and a laryngoscope, whenever an operation on the thyroid is being done, regardless of the type of anesthesia employed. This prevents delay in establishing the airway, the need for which may occur suddenly in occasional cases.

*Intravenous Anesthesia.*—During the past ten years the use of intravenous pentothal sodium anesthesia has been increasing for all types of surgery. Many thyroid surgeons favor its use in this field. From certain standpoints it is suitable, since it does not untowardly affect the metabolic processes of patients suffering from thyroid disease. The comparative freedom from nausea and vomiting following pentothal sodium anesthesia is desirable and it may be used with any amount of oxygen the patient may require. On the other hand, certain technical factors may enter the picture. If pentothal sodium is used as the sole anesthetic agent, mechanical obstruction of the upper part of the respiratory tract or obstruction due to laryngeal spasm can occur. Since the laryngeal reflexes probably will be still active, it may be difficult to insert an intratracheal tube without trauma, if the need arises. Certain patients suffering from thyroid disease who are unusually hyperactive may require large amounts of the drug, which may result in a prolonged post-

operative sleep, accompanied by restlessness or excitation during recovery. All these side effects are undesirable.

For those who wish to take advantage of the desirable features of intravenous anesthesia, we feel that its use as an adjunct to other methods of anesthesia produces the best results. There are a number of possibilities that may be worthy of consideration. Pentothal sodium anesthesia provides a rapid and pleasant induction to inhalation anesthesia for patients who are upset and nervous. For certain patients this is carried out in their own room before they are taken to the operating room. If pentothal sodium is used as a supplement to local or regional anesthesia only minimal amounts of the intravenous agent may be required and it may be possible to arouse the patient at the end of the operation. When this method is used alone or as a supplement to other methods, oxygen or a mixture of 50 per cent nitrous oxide and 50 per cent oxygen should be administered during the course of the intravenous anesthesia. Combinations of pentothal sodium and the gaseous anesthetic agents may often prove useful when the use of ether is inadvisable. When the upper portion of a patient's respiratory tract becomes partially obstructed, helium-oxygen mixtures can be utilized to facilitate oxygenation of the patient.

#### COMMENT

Modern anesthetic agents and methods have been important in improving the preoperative, operative, and postoperative management of patients undergoing operations on the thyroid. The choice of anesthesia for these patients has been broadened in recent years so that there are many different anesthetic approaches to the various problems presented by the patient suffering from goiter. In order to obtain the fullest benefit from the choice of anesthesia, the problems of the individual case should be weighed preoperatively by the surgeon and the anesthesiologist. By such collaboration the surgeon can supply the anesthesiologist with information relative to the surgical requirements and possible complications. In this way, methods of anesthesia may be chosen which offer the patient the minimum of toxic effects from the anesthetic agent and which, at the same time, provide continuous control of the patient and of the complicating factors which may arise.

## TECHNIQUE OF THYROIDECTOMY

FRANK H. LAHEY, M.D., BOSTON, MASS.

THE technique of subtotal thyroidectomy for exophthalmic goiter and toxic adenoma, as well as that of removal of a discrete adenoma, intrathoracic goiter, and the isthmus for constricting thyroiditis, is best demonstrated, I believe, by illustrations. Any technical procedure, such as a surgical operation, can be understood more adequately and more quickly, with less likelihood of misunderstanding, if it can be visualized. Since the accompanying drawings with their descriptive legends clearly show the various steps of the procedures, a lengthy discussion will be unnecessary.

The methods here presented are based upon the removal of over 23,000 goiters. These technical procedures are the result of progressive refinement of our technique prompted by added experiences and constantly widening contacts with all aspects of thyroid disease. While many of the fundamental steps were designed by me, some have been modified by other members of the Department of Surgery of the Lahey Clinic. These procedures, which are standard in this institution, have stood the test of time, numbers, and repeated follow-up studies.

### COMMENT

While this presentation deals solely with surgical technique, I cannot conclude it without calling attention to the fact that the operative procedure is but one of several factors concerned in a successful thyroidectomy. Experienced judgment in the preparation of these patients and the decision concerning the optimal time for operation are of equal, if not greater, importance than the technical procedure. The same may be said of anesthesia and postoperative management, since without experience and judgment in these fields, a thyroidectomy, although scientifically executed, may have an unsatisfactory result. In no other field of surgery is a greater variety of skill and experience needed to obtain a good result and a low mortality. Here the knowledge of the cardiologist, endocrinologist, internist, anesthetist, and surgeon may be most advantageously combined in obtaining a satisfactory postoperative result.

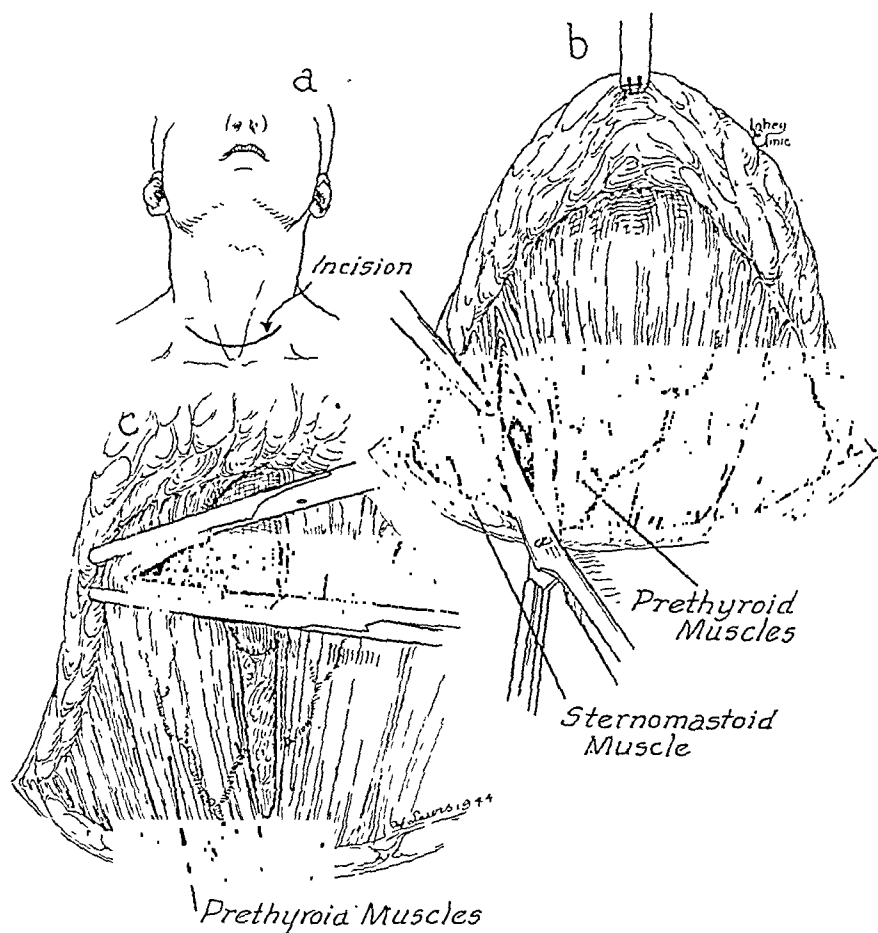


Fig. 1.—*a*, The curve employed in goiter incisions in this Clinic. With the chin elevated, the chest thrown forward, and the neck in the forward goiter position, the incision is placed a little higher than ultimately desired. When the chin comes down and the chest is lowered, the incision descends about 1 inch.

*b*, The height to which the skin flap is elevated. Good exposure of the thyroid gland requires elevation of the skin flap up to and above the level of the notch in the thyroid cartilage. This permits adequate exposure of the superior thyroid artery and veins at the upper pole of the thyroid gland where they enter, so that they may be ligated well off the thyroid gland. The sternomastoid muscle is being separated from the prethyroid muscle. The former will then be retracted so that when the clamps are applied across the prethyroid muscles, as in *c*, they can be clamped well out and wider exposure obtained.

*c*, The high level at which the prethyroid muscles are cut. The innervation remains undisturbed. The future level will be well up under the skin flap where it will not interfere with closure of the skin incision or complicate its healing. A thyroidectomy can be done more safely and with better exposure if the prethyroid muscles are cut. Although thousands of prethyroid muscles have been cut and sutured at the Lahey Clinic, no deformity, disfigurement, or dysfunction has resulted.

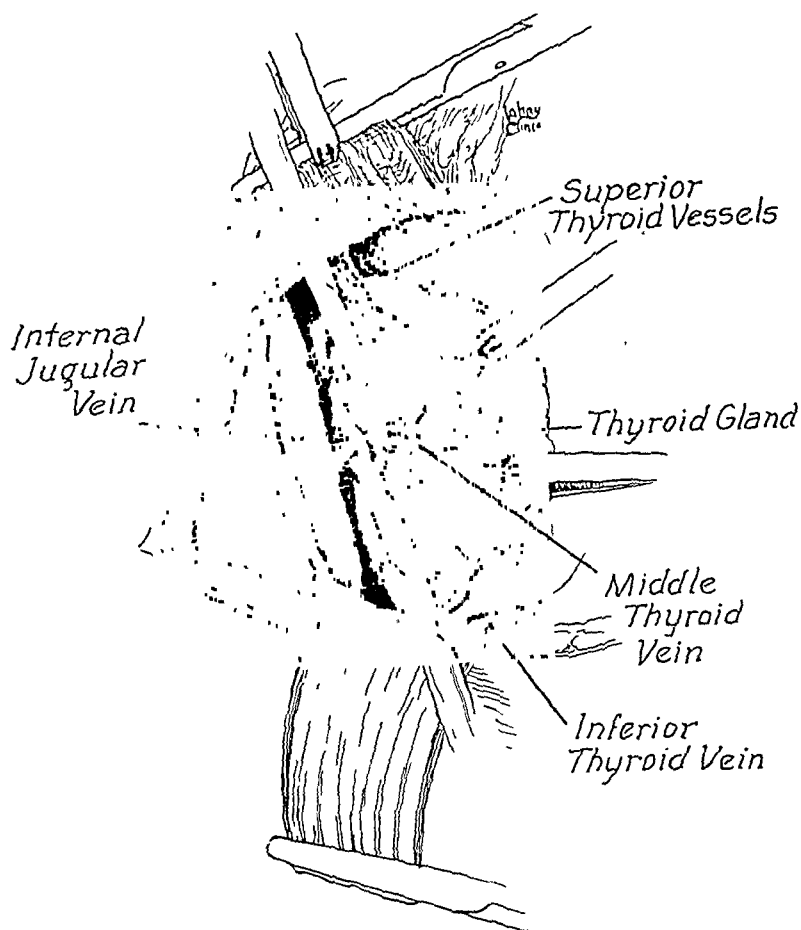


Fig. 2.—The internal jugular vein, and the middle thyroid vein as it enters the middle of the thyroid gland. The first step after exposure of the thyroid gland is severing the middle and inferior thyroid veins, which facilitates mobilization of the thyroid gland up out of its bed. Note the excellent visualization of the superior thyroid vessels when the skin and muscle flaps are elevated adequately. The double hooks, specially modified in this Clinic, lift the gland up out of its bed in order to obtain adequate exposure.

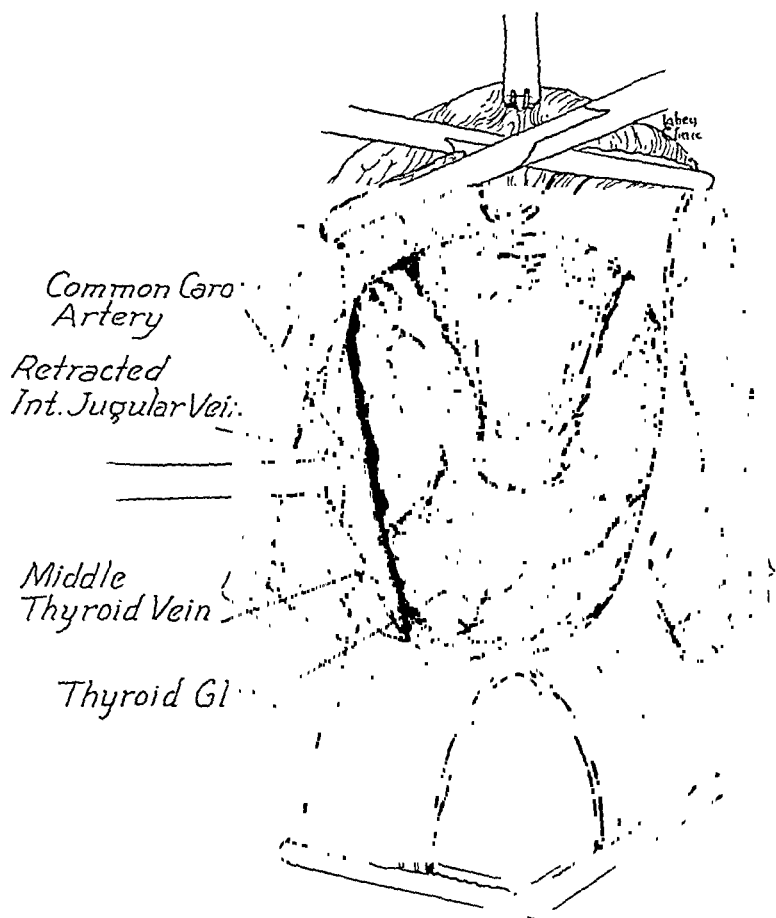


Fig. 3.—After the middle and inferior thyroid veins are ligated and severed, the internal jugular vein is retracted, thus exposing the common carotid artery, beneath which, with the gland lifted out of its bed, the inferior thyroid artery can be demonstrated. As a result of elevation of the prethyroid muscles above the level of the notch of the thyroid cartilage, the upper pole of the gland with its entering vessels is clearly exposed.

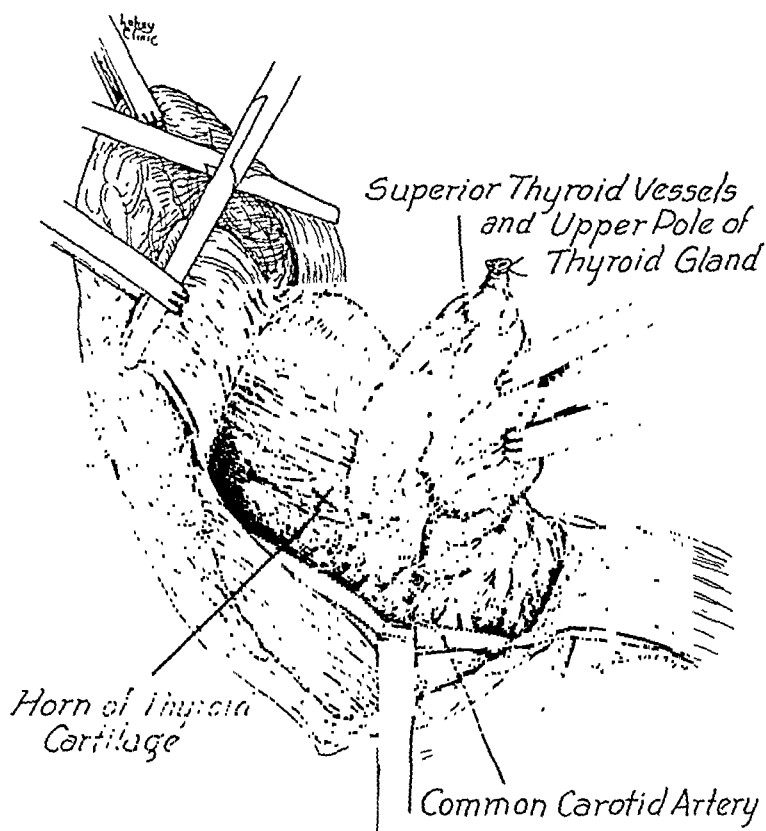


Fig. 4.—The upper pole of the thyroid gland is mobilized after ligation of the superior thyroid vessels. The attachment of the thyroid lobe to the larynx has been freed, thus making possible a more radical removal of thyroid tissue (Fig. 5). Note the level of the horn of the thyroid cartilage. At this point the recurrent laryngeal nerve becomes intralaryngeal, so that above this there is no danger of injury. Note the retraction of the common carotid artery by means of which the inferior thyroid artery can be found and ligated.



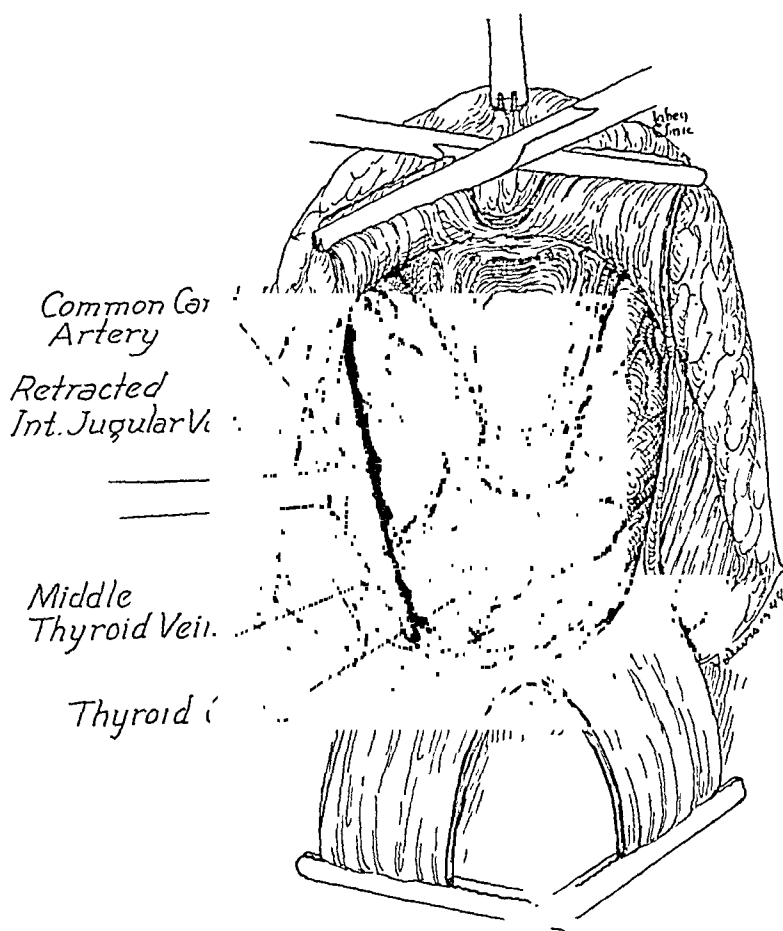


Fig. 3.—After the middle and inferior thyroid veins are ligated and severed, the internal jugular vein is retracted, thus exposing the common carotid artery, beneath which, with the gland lifted out of its bed, the inferior thyroid artery can be demonstrated. As a result of elevation of the prethyroid muscles above the level of the notch of the thyroid cartilage, the upper pole of the gland with its entering vessels is clearly exposed.

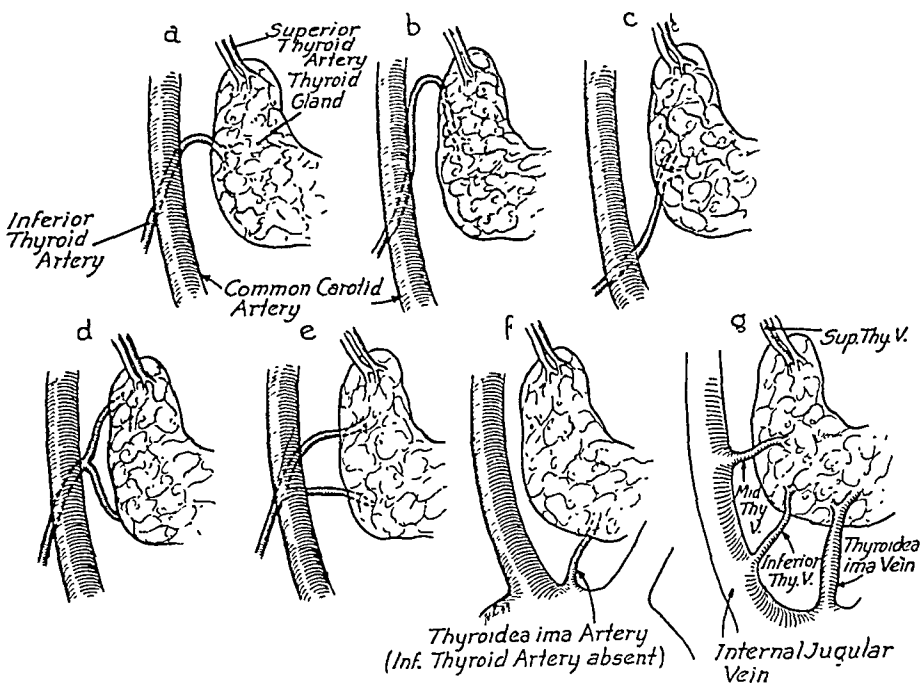


Fig. 6.—The various types and positions of the inferior thyroid artery.

*a*, A common type of inferior thyroid artery enters directly into the gland.

*b*, The inferior thyroid artery arches upward and sometimes descends behind the thyroid gland to enter it, the arch sometimes being as high as the superior pole.

*c*, The inferior thyroid artery which extends from below upward is the type most difficult to demonstrate. The surgeon is apt to think that the artery is absent because it is not in the most common positions (*a*, *b*, *d*, and *e*). Demonstration of this type of inferior thyroid artery requires elevation of the lower pole of the thyroid gland well out of its bed, retraction of the common carotid artery at a low point, and careful dissection of the deep cellular tissue under good light.

*d*, A common type of inferior thyroid artery, which divides well out from the gland.

*e*, The same type as *d*, with division of the inferior thyroid artery well behind the common carotid artery. Either the upper or the lower branch only may be demonstrated and ligated, and the second branch may be overlooked. This results in continued bleeding in the gland, which is not controlled or explained until the second branch is found and ligated.

*f*, The inferior thyroid artery is absent, the blood supply coming from a thyroidea ima.

*g*, The common location of the thyroid veins (middle, inferior, and ima). Complete mobilization of the thyroid gland and turning it up out of its bed (Fig. 5) require that all venous attachments between the thyroid gland and the internal jugular vein be ligated and severed.

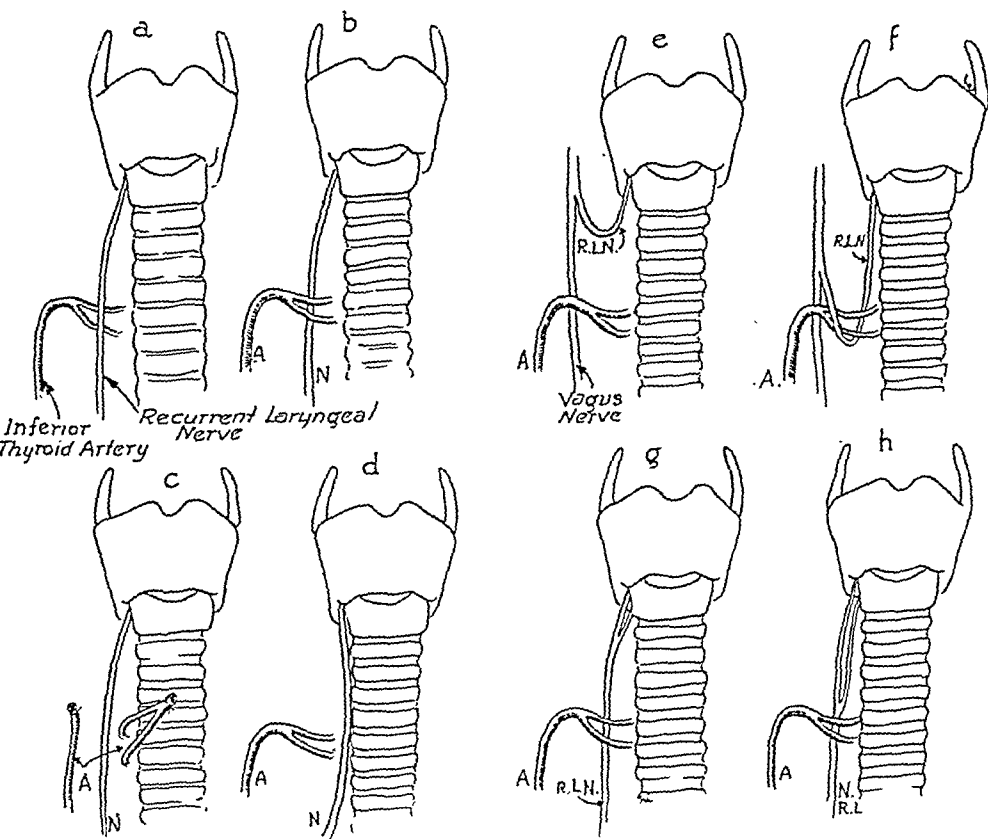


Fig. 7.—The locations and abnormalities of the recurrent laryngeal nerve.

a, The recurrent laryngeal nerve passes over the inferior thyroid artery. A nerve in this location is demonstrated and also injured more easily than the one which passes under the inferior thyroid artery. When the thyroid gland is lifted out of its bed, the nerve also is lifted up as the artery is pulled upward in the mid-portion of the gland.

b, The most common position of the recurrent laryngeal nerve. The inferior thyroid artery must be found first, and then the nerve is demonstrated as it passes under or over it.

c, The inferior thyroid artery is severed and ligated at both ends. In a difficult procedure this facilitates demonstration of the recurrent laryngeal nerve from its point of emergence in the mediastinum to its point of entrance into the larynx.

d, The position of the recurrent laryngeal nerve in intrathoracic goiter. As the thyroid adenoma descends into the mediastinum, it tends to push the recurrent laryngeal nerve against the trachea until it is sometimes so adherent that demonstration is difficult unless this occasional anomalous position is recognized.

e, The recurrent laryngeal nerve does not descend into the mediastinum, but comes straight across from the vagus to enter the larynx beneath the inferior constrictor muscle.

f, The recurrent laryngeal nerve descends as far as the inferior thyroid artery and ascends behind it to its point of entrance into the larynx.

g, Extralaryngeal division of the recurrent laryngeal nerve.

h, Extralaryngeal division extending as low as the inferior thyroid artery.

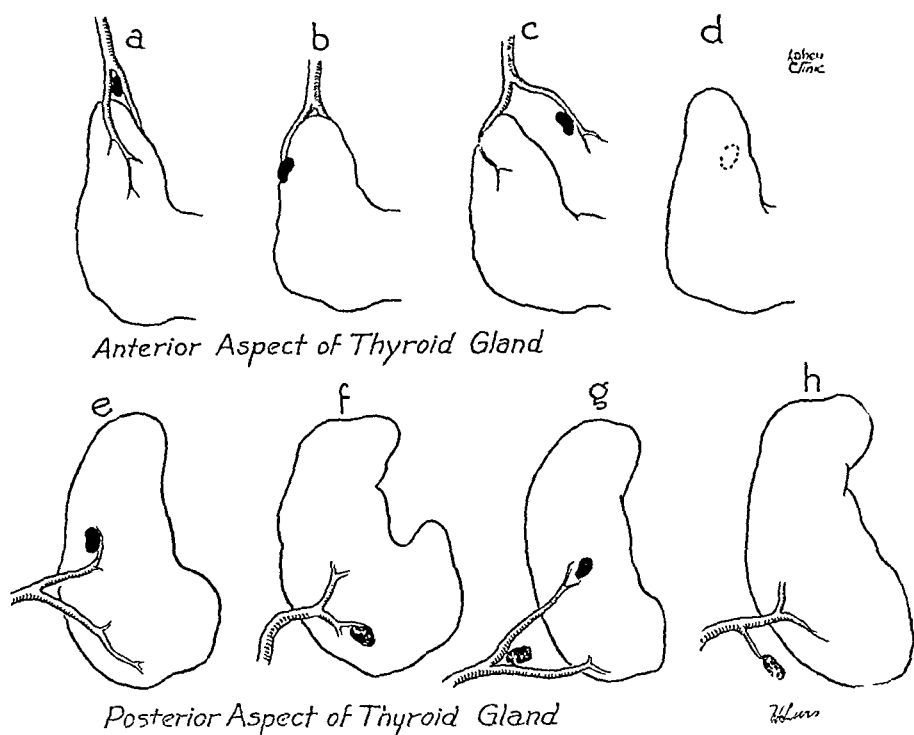


Fig. 8.—The anterior and posterior aspects of the thyroid gland showing the various positions in which a parathyroid gland has been demonstrated. *d*, The dotted line shows the parathyroid gland against the larynx. This type can easily be removed unless it is carefully visualized as the upper pole is pulled away from the larynx. *h*, The type of parathyroid gland with a separate terminal branch of the inferior thyroid artery. If an adenoma of the parathyroid gland cannot be found, the entire course of the inferior thyroid artery should be carefully demonstrated, preserving all its branches. If a branch comes off the main trunk downward, it should be followed, since it will often lead to a parathyroid adenoma in the mediastinum.

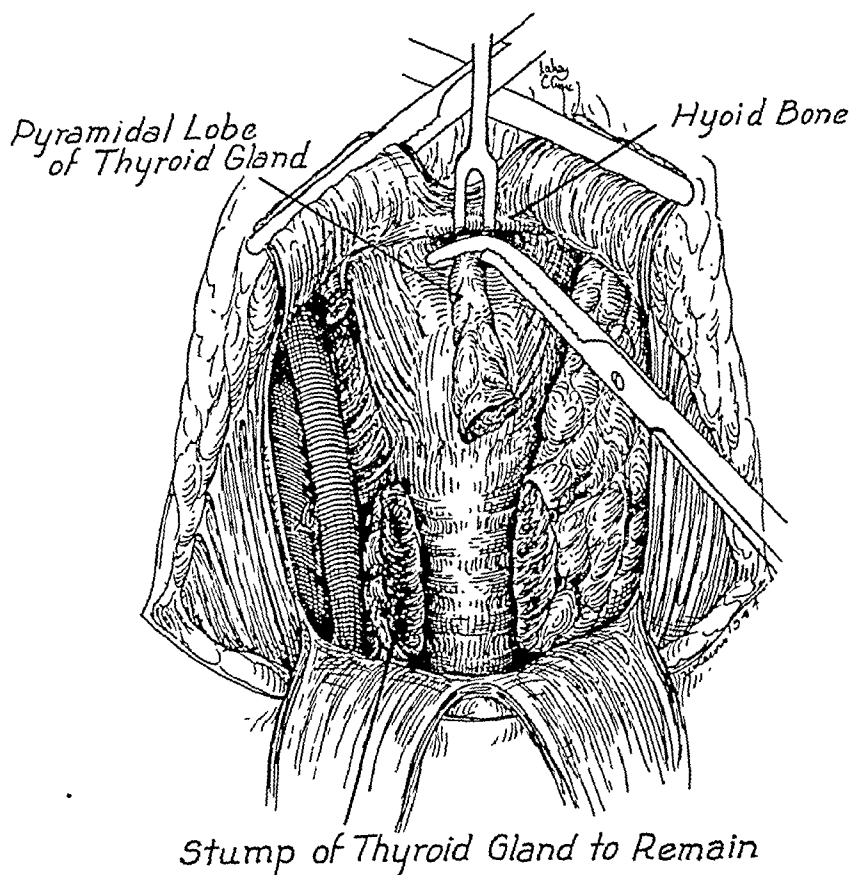
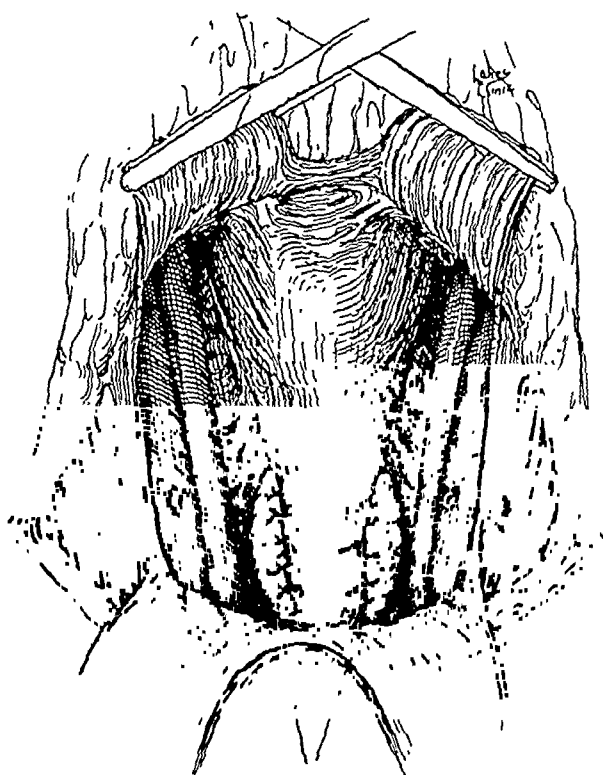


Fig. 9.—The removal of the pyramidal lobe, which is present in a large number of cases. If the pyramidal lobe is not removed in a patient with an exophthalmic goiter, it may enlarge sufficiently to cause persisting hyperthyroidism and an unsightly tongue of hyperplastic tissue in the central portion of the neck. Therefore, in subtotal thyroidectomy a careful search should be made for the pyramidal lobe, following it well up above the notch of the thyroid gland to the point where it disappears or ceases at the hyoid bone. In our experience in the removal of the pyramidal lobe, section of the hyoid bone has been unnecessary.

On the right side the superior thyroid artery and vein have been ligated. The tie here is often so close to where the vessel is cut that with coughing it can blow off. When the operation is completed, therefore, this ligated stump of the superior thyroid artery and vein should be regrasped and ligated a second time above the first ligature. When the superior thyroid artery is thus twice ligated and the inferior thyroid artery is ligated as a trunk (Fig. 5), serious secondary arterial hemorrhage is unlikely.



*Remnants of Thyroid Gland  
sutured to Trachea*

Fig. 10.—Completed reconstruction of the thyroid gland. The small stumps of thyroid tissue shown behind the dotted line in Fig. 5 are so sutured against the trachea with fine 00 catgut that the oozing surface is buttressed against the trachea. All bleeding of an oozing character is controlled, and drainage is unnecessary. Again, note the height to which the skin and muscle flaps are elevated in order to obtain high exposure.

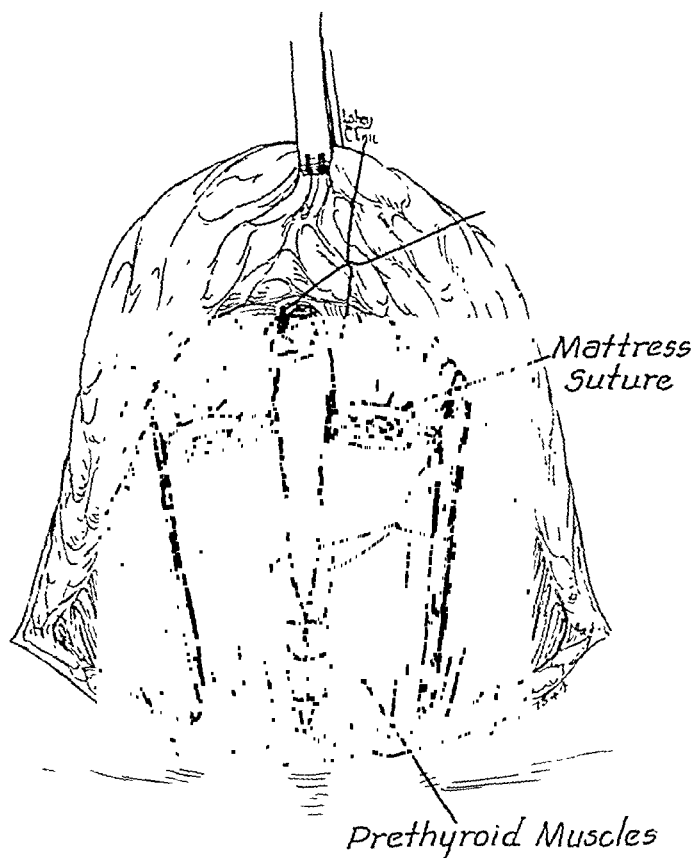


Fig. 11.—The method of suturing muscles with mattress sutures, the height to which they are sutured, and the accurate closure of the muscles in the midline are shown. Unless the muscles are accurately closed in the midline, the skin flap will become adherent to the trachea, will ascend and descend with swallowing, and will thus result in an ugly disfigurement. The sutures are well above the point of innervation and do not involve the same level as the skin suture.

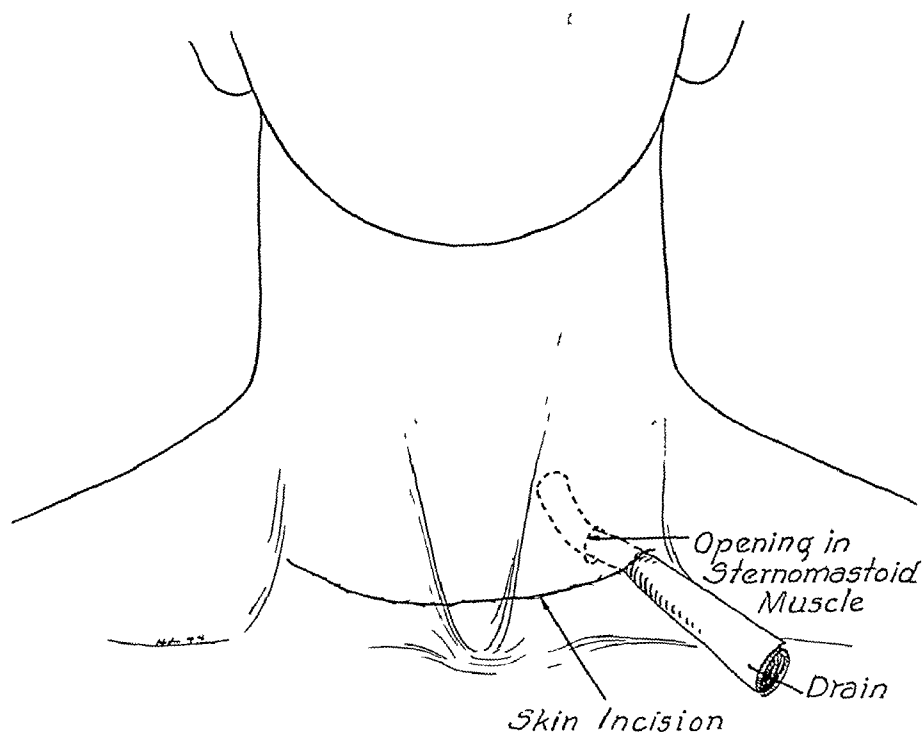


Fig. 12.—Drainage occasionally is necessary in recurrent hyperthyroidism after second stage hemithyroidectomy. The drain is not inserted in the midline in a counterincision, as has often been proposed, because this produces disfigurement and the scar cannot be covered with a necklace. It is placed at the end of the skin incision, which will close when the drain is withdrawn, and pierces the sternomastoid muscle. Since it is at the outermost portion of the wound, adhesions will not occur between the trachea and the skin. When the drain is withdrawn from its opening in the sternomastoid muscle, the muscle will then be interposed in the scar in the bed of the thyroid gland to prevent fixation of the scar of the skin to the thyroid bed scar.



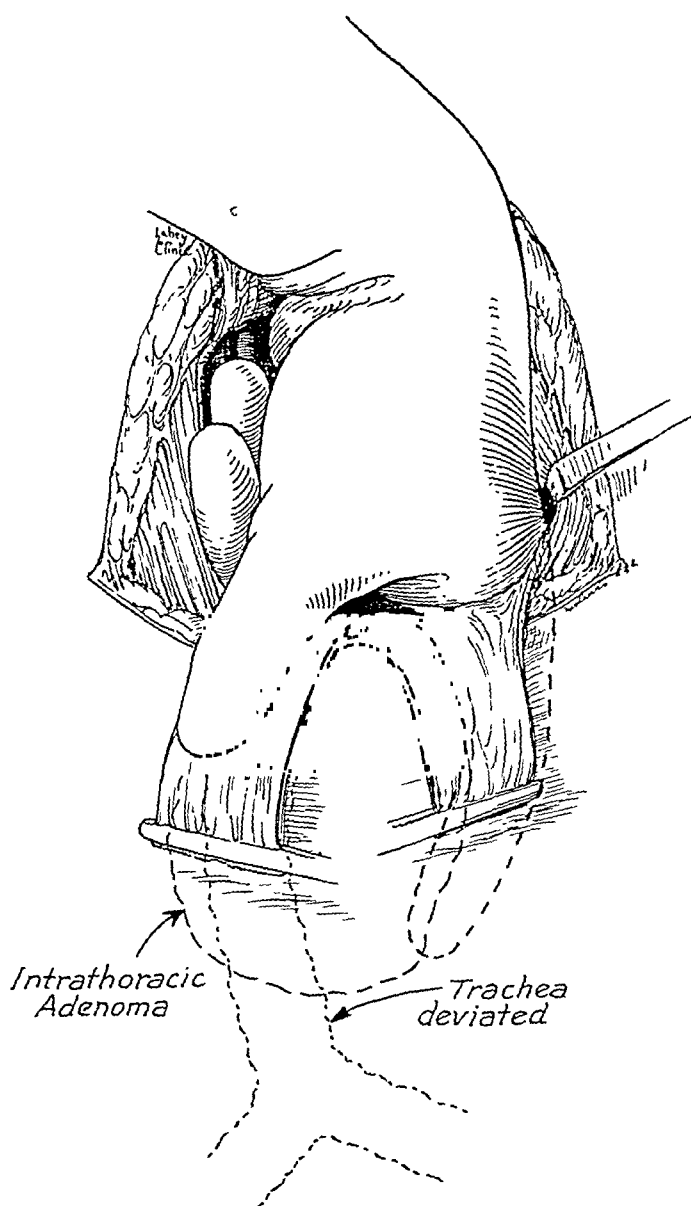


Fig. 13.—The method of freeing an intrathoracic goiter from the mediastinal tissue. Note that the index finger is inserted into the mediastinum outside the capsule of the adenoma and is swept around until the adenoma is freed from the pleura and cellular tissue in the mediastinum. This is the first step in removing an intrathoracic goiter which is often of such diameter that it cannot be made to pass through the aperture of the superior thoracic strait.

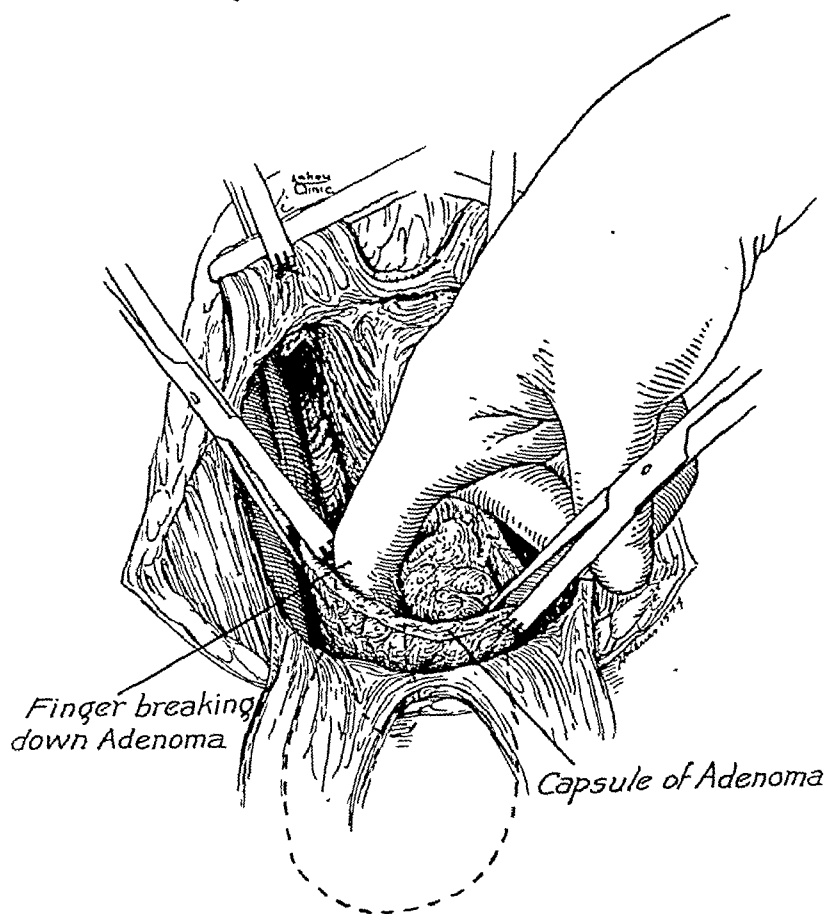


Fig. 14.—After the upper third or half of the adenoma has been freed from the surrounding cellular tissue and pleura in the mediastinum (Fig. 13), it is lifted with double hooks just above the clavicle and its top is incised. This leaves the soft contents exposed. Unless the tumor is carcinomatous and so of solid consistency, the index finger can be inserted into the center. Its contents, which are usually seminecrotic or semicystic, can be broken down and scooped out, and its fluid sucked out, thus decreasing its diameter. With gradual traction upward on the double hooks, which are inserted in the capsule, the adenoma is lifted and further separated with the index finger outside of the capsule (Fig. 13), freeing it from the pleura, thus further breaking down its center, with additional delivery. In this manner, enormous intrathoracic goiters can be delivered from the mediastinum without removing the manubrium or the clavicle.

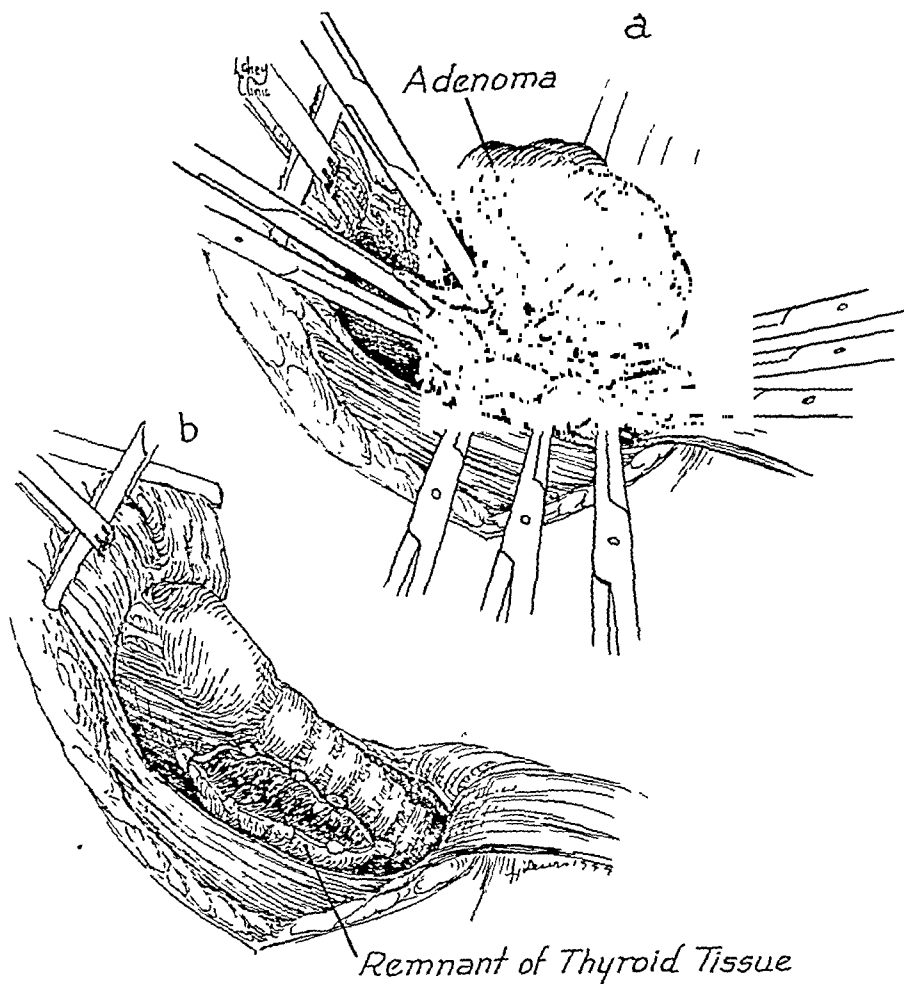


Fig. 15.—The method of removing a discrete adenoma of the thyroid gland is different from a subtotal thyroidectomy for exophthalmic goiter.

*a*, An Ochsner clamp with another small clamp over it is placed on the upper portion of the nonadenomatous part of the gland and in the same manner on the lower portion. Next clamps are placed along the outer side of the adenoma, where normal thyroid tissue covers it, and this layer is cut, so that the adenoma literally can be shelled out of the body of the thyroid tissue. As the adenoma is shelled out toward the midline, a small envelope of thyroid tissue of varying thickness is retained along the trachea until all the adenoma is excised.

*b*, The edges of the thyroid gland can be brought together to reconstruct a good lobe of thyroid tissue.

The recurrent laryngeal nerve is not shown, but in this operation, as in subtotal thyroidectomy for exophthalmic goiter, the inferior thyroid artery is ligated to protect against later secondary hemorrhage, and the recurrent laryngeal nerve is demonstrated. The wisdom of dissecting the recurrent laryngeal nerve in the removal of a discrete adenoma often has been questioned, but in this operation it is even more important than in the removal of an exophthalmic goiter. A discrete adenoma often so completely occupies the substance of the thyroid gland that but a thin shell of normal thyroid tissue remains between the back wall of the discrete adenoma and the nerve. Thus, the recurrent laryngeal nerve is in close contact with this thin shell of tissue and with the capsule of the adenoma. Because of this, it is easy to penetrate the thin shell of thyroid tissue behind the adenoma and thus unknowingly pinch the recurrent laryngeal nerve.

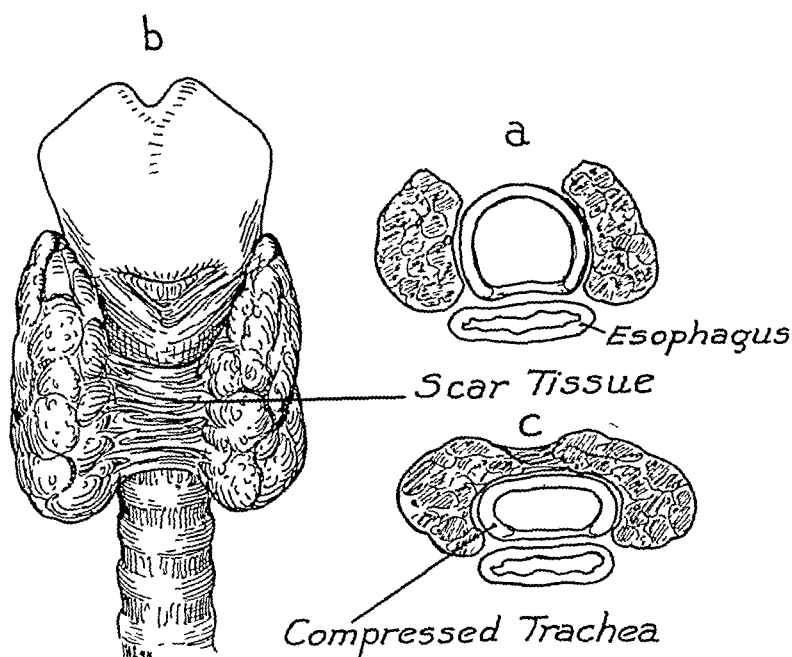


Fig. 16.—The incorrect method of removing the isthmus in patients with thyroiditis who complain of constriction of the trachea due to organization of round-cell infiltration. No attempt has been made to prevent scar tissue formation between the two cut ends of the remaining lobes; thus contraction causes further constriction.

a, The isthmus has been removed.

b, The development of scar tissue between the two remaining lobes over the trachea.

c, Compression of the trachea results from contraction of scar tissue replacing removed isthmus and joining the two lateral lobes. When this occurs the trachea sometimes is decreased sufficiently in size to interfere seriously with the intake of an adequate amount of oxygen.

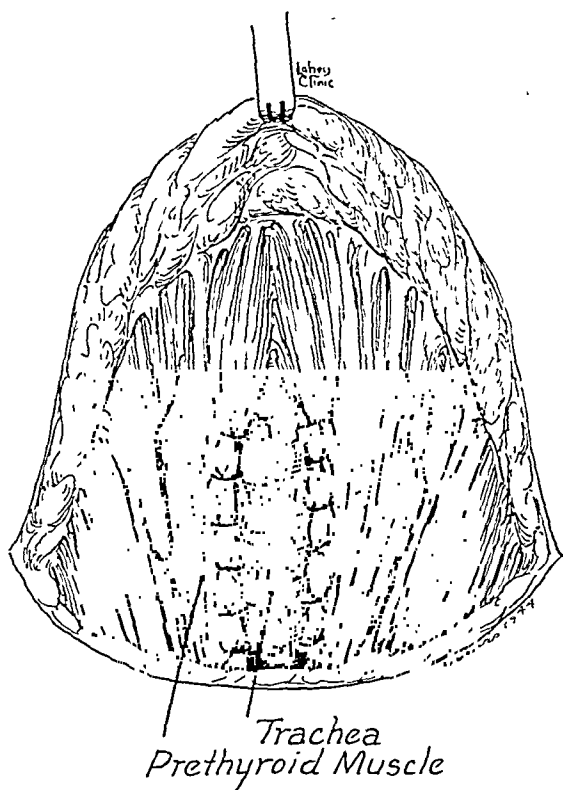


Fig. 17.—The correct method of removing the isthmus for constricting thyroiditis. The suture of the prethyroid muscles is shown over the stump of thyroid tissue on each side where the isthmus has been removed. The prethyroid muscles are attached to the trachea, thus completely segregating the two segments of thyroid gland beside the trachea and preventing the formation of scar tissue between them.

Surgery is rarely necessary in thyroiditis. Occasionally, however, as the result of the entire trachea being grasped by an enlarged thyroid involved in thyroiditis, a considerable sense of constriction results. This can be relieved by removal of the isthmus. Further constriction can be avoided by suturing the prethyroid muscle to the trachea over the sutured ends of the remaining thyroid tissue in each lobe, thus preventing the formation of any scar tissue between the two separated lobes.

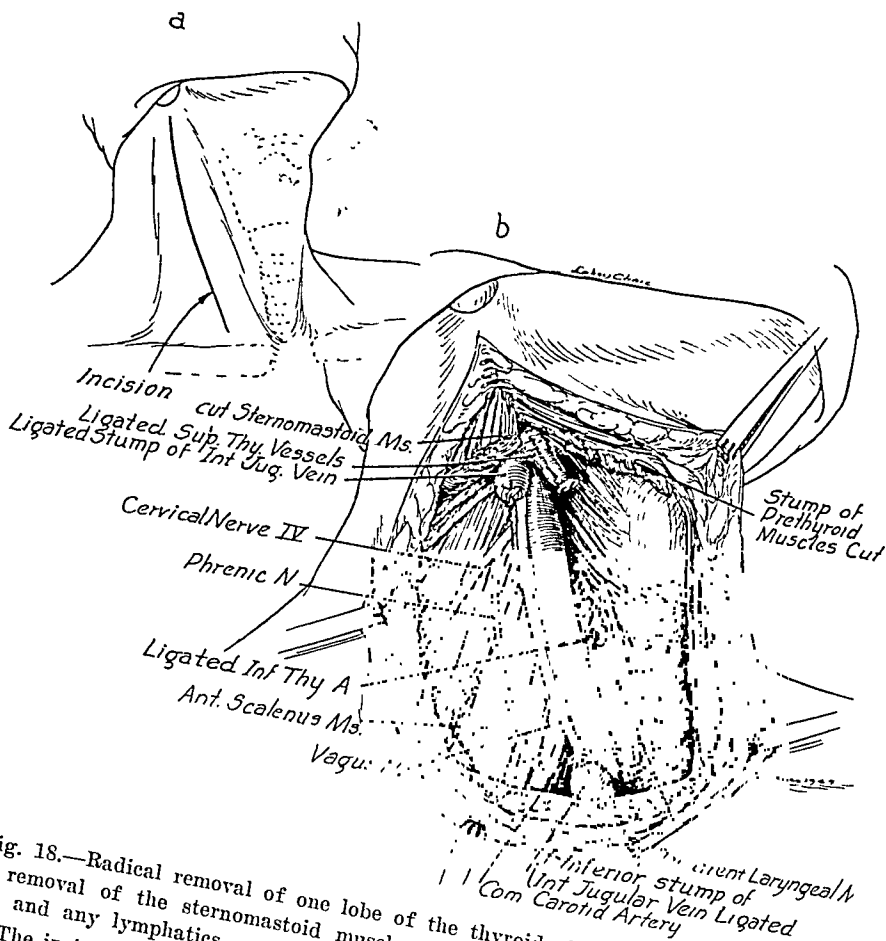


Fig. 18.—Radical removal of one lobe of the thyroid gland for cancer, together with removal of the sternomastoid muscle, the internal jugular vein, the thyroid veins, and any lymphatics.

a, The incision and b, the anatomic relationships following radical removal of one lobe and the isthmus of the thyroid gland for an adenoma. Malignancy had penetrated the capsule of the adenoma and had involved the parenchyma of the thyroid gland. The incision can be longitudinal or can be carried across the neck as a fish-hook type.

Since malignancy of the thyroid gland has a definite tendency to invade veins, it has always been our practice, when carcinoma has penetrated the capsule of an adenoma and involved the parenchyma of the gland on one side, to do a radical dissection, ligating the internal jugular vein high and low and severing the sternomastoid muscles high and low. The entire sternomastoid muscle, tributary veins, regional lymph nodes, and the entire right lobe and isthmus of the thyroid gland containing the malignant degenerated adenoma are then removed in one block. Included with the block of removed tissue are the prethyroid muscles.

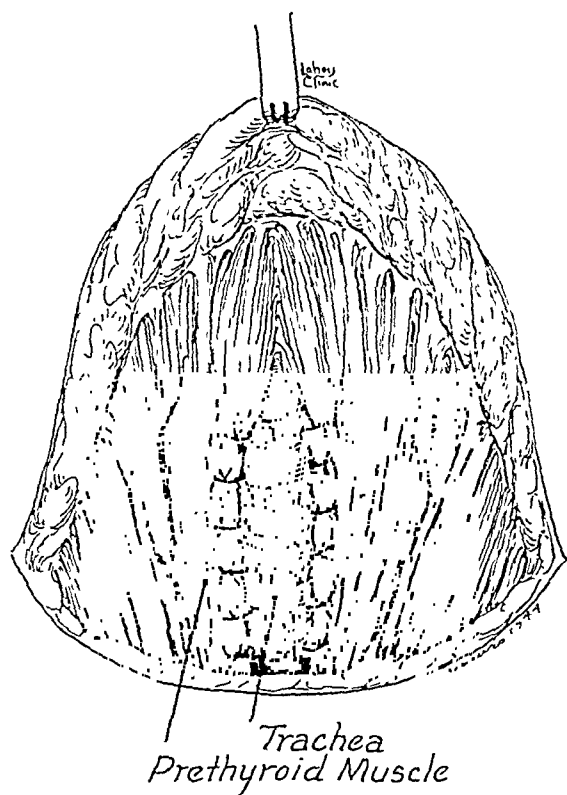


Fig. 17.—The correct method of removing the isthmus for constricting thyroiditis. The suture of the prethyroid muscles is shown over the stump of thyroid tissue on each side where the isthmus has been removed. The prethyroid muscles are attached to the trachea, thus completely segregating the two segments of thyroid gland beside the trachea and preventing the formation of scar tissue between them.

Surgery is rarely necessary in thyroiditis. Occasionally, however, as the result of the entire trachea being grasped by an enlarged thyroid involved in thyroiditis, a considerable sense of constriction results. This can be relieved by removal of the isthmus. Further constriction can be avoided by suturing the prethyroid muscle to the trachea over the sutured ends of the remaining thyroid tissue in each lobe, thus preventing the formation of any scar tissue between the two separated lobes.

## DRAINAGE IN THYROIDECTOMY

DONALD GUTHRIE, M.D., F.A.C.S., AND  
IRWIN SCHIMMEL, M.D., SAYRE, PA.

THE problem of drainage versus nondrainage in thyroidectomy is one which always arouses debate among surgeons. Ever since the days of Kocher, the father of modern thyroid surgery, drainage was practiced by practically all of the early American surgeons with the exception of Halsted, who advocated the use of silk and who believed that drainage of the wound was unnecessary. Drainage was necessary because heavy catgut was employed to secure hemostasis. As a result of the exudative response of the tissues to catgut, these wounds all drained freely for a considerable length of time.

When catgut was used routinely at the Guthrie Clinic, all of the wounds were drained with one or more rubber tubes which were placed in the goiter bed and were allowed to remain about forty-eight hours. Large substernal and intrathoracic cavities were drained with three or four tubes which remained in place for four or five days. All of the wounds continued to drain approximately fifteen days, necessitating a hospital stay for the patient of at least sixteen days after the operation.

Before discontinuing the catgut technique, an attempt was made to use finer catgut in order to eliminate drainage. However, this was unsuccessful because of the tissue response to the absorbable suture material. A compromise technique using fine catgut to suture the remnant and silk for all ligatures was tried; with this method we were able to close 62 per cent of the wounds without drainage. However, this technique was soon supplanted by an all-silk thyroidectomy. With the advent of the nonabsorbable suture technique, wound drainage became unnecessary and, we believe, fraught with risk because of the danger of secondary infection through the open portion of the wound.

Following the report of Meade and Oschsner, in 1940, in which cotton as a suture material was proved to cause less tissue reaction and earlier healing than silk, cotton replaced silk as the nonabsorbable suture material for all thyroidectomy wounds. With this technique, the patient's temperature in the average case is usually normal within forty-eight hours. One-half of the clips are removed within twenty-four hours and the remainder at the end of forty-eight hours. The wound dressing may be discarded with safety at the end of ninety-six hours and the average postoperative stay in the hospital is reduced to



nine days. No further dressings are necessary and six days are removed from the post-thyroidectomy hospitalization.

In reviewing our results since the adoption of the nondrainage technique, we have found that in a series of 580 cases, it was necessary to use a drain in only 8. Furthermore, none of these drains was placed in the goiter bed, all being inserted under the skin flap as advocated by Coller. In this series there were three wound infections, two being of a minor nature. In one case the skin edges opened completely and a secondary closure was necessary. An occasional patient will require the removal of a sterile cotton knot. However, since we have used the very fine No. 80 cotton in the skin flap, this procedure has been necessary in but two or three patients.

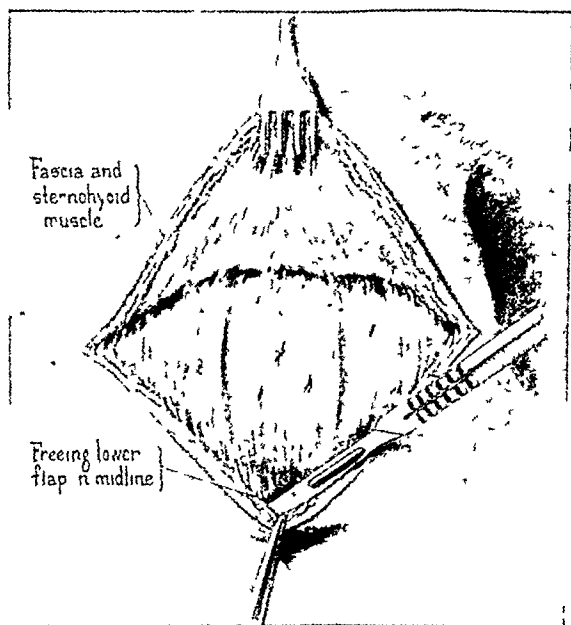


Fig 1—Freeing the lower flap in the midline only over the suprasternal notch (Illustrations by permission of Surg. Gynec & Obst., from "A Technique of Thyroidectomy Permitting the Use of Silk" by Donald Guthrie and Merle J. Brown 68: 801-809, 1939.)

Mediastinitis is feared by many surgeons following the removal of substernal or intrathoracic goiters if drainage is not employed. A few of them pack these cavities with gauze. Such a procedure would seem to insure secondary infection rather than to prevent it. We have not used drainage in any of these cases and have seen no untoward effects as a result. Two of our patients, in whom drainage was done when catgut was used, developed mediastinitis due to secondary infection and died as a result.

There are a few technical points which must be employed if the surgeon is to use the nondrainage method successfully. In the first place all dissection must be sharp with a constant regard for tissue

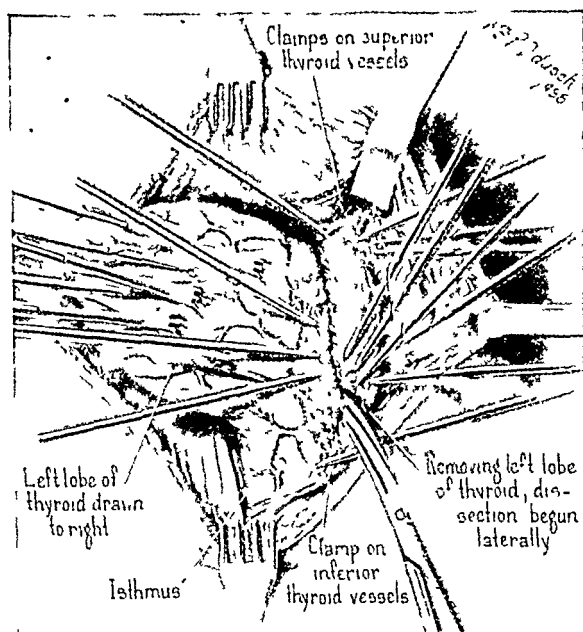


Fig 2.—Dissection of the lobe continued to show what should be the size of the thyroid remnant that is to be left in situ

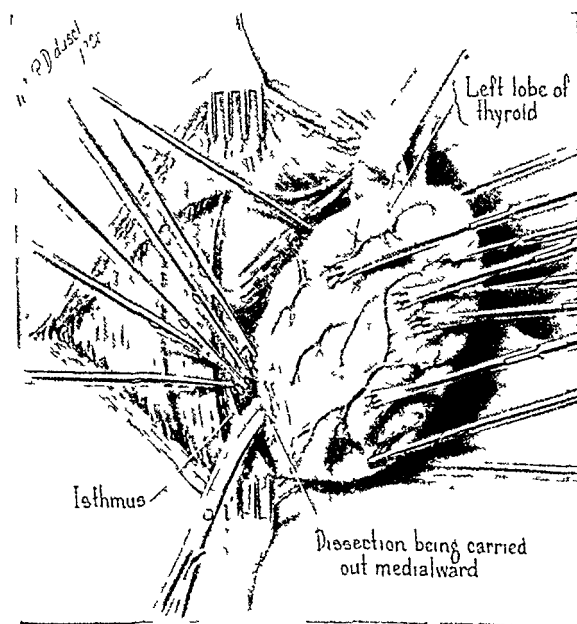


Fig 3.—Dissection of the lobe from the trachea showing remnant of the gland left along the trachea

because blunt dissection encourages edema and wound exudation. Mass ligatures must not be employed and hemostasis must be absolute. It is obvious that wide dissection of the lower skin flap is unnecessary for exposure and merely provides additional dead space where serum may collect (Fig. 1). In accordance with the principles outlined by Lahey, after all the vessels have been ligated, the remnant which has

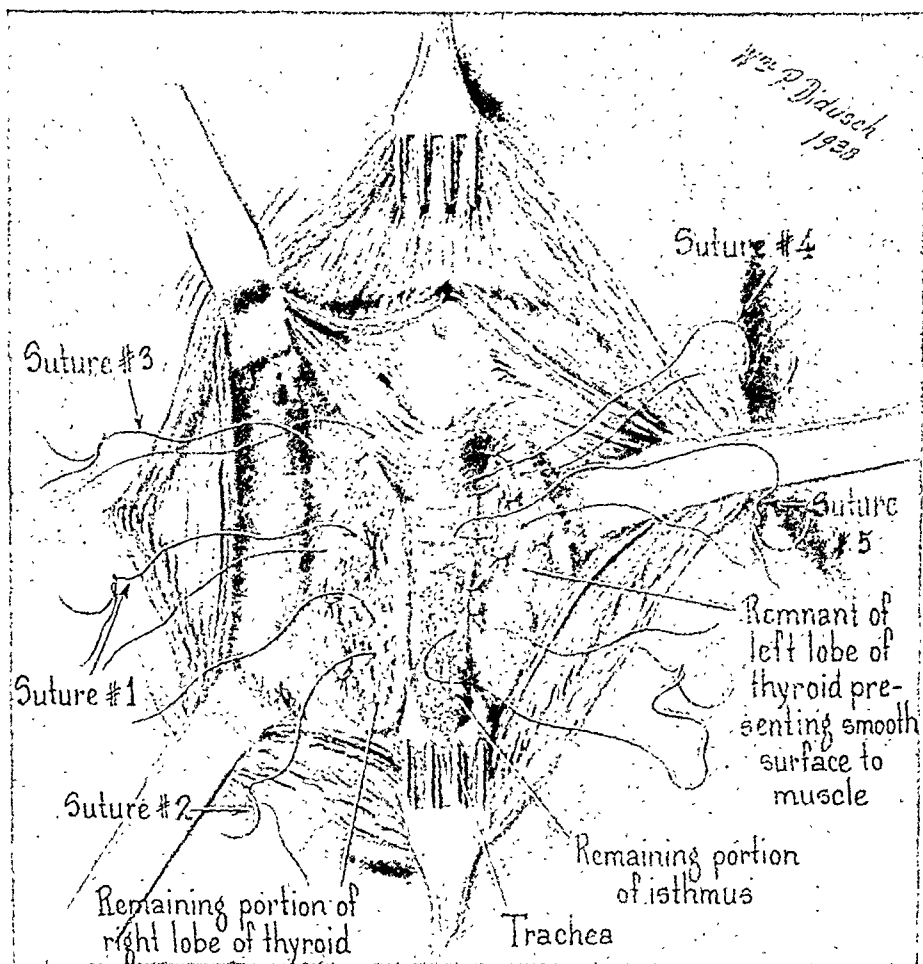


Fig. 4.—Method of controlling hemorrhage from the remnant by two rows of the interrupted fine silk sutures placed at different levels in the long axis of the neck. Interrupted sutures are placed through the edges of the remnant and the fascia and the thyroid tissue of the trachea inverting the outer surface of the remnant to conceal its incised surface.

been carefully plotted is rotated medially toward the trachea. Its lateral portion is then sutured to the small bit of thyroid gland which has been intentionally left attached to the trachea (Figs. 2 and 3). This brings the cut and oozing surface of the gland against the trachea, providing a valuable adjunct in hemostasis (Fig. 4). A dry wound is the sine qua non of the nondrainage method of thyroidectomy. In ad-

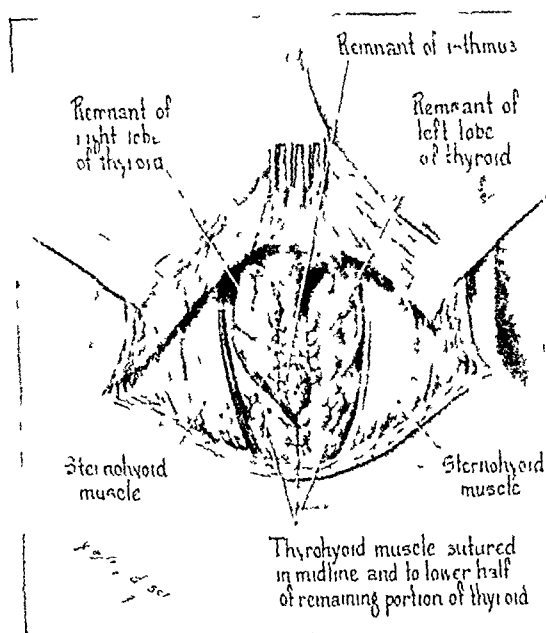


Fig 5—Sternohyoid muscles are sutured at the midline and to the lower portion of the remnant.

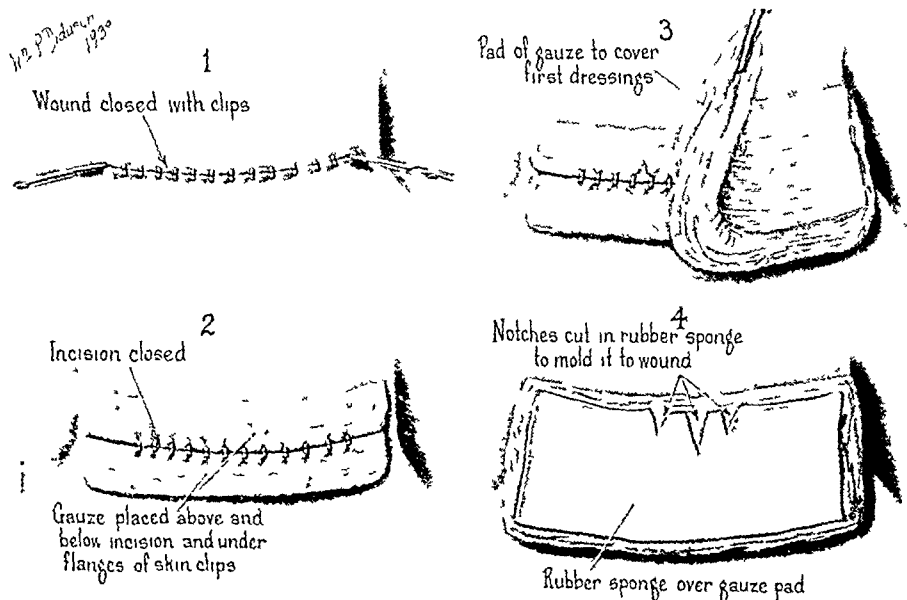


Fig 6—Illustrating the method of dressing the wound

dition, we believe that suturing the right and left sternothyroid muscles together in the midline and, if necessary, to the base of the remnant, is valuable in further insuring against oozing and bleeding (Fig. 5). The sternohyoid muscles are sutured in the midline and then the flap is carefully inspected to be certain that there is absolute hemostasis.

As an added precaution to prevent flap oozing and to aid in obliterating dead spaces, we employ a notched rubber sponge over the wound. This is held in place by two one-inch adhesive strips and the entire neck is wrapped with wide gauze bandage. We employ this technique in all cases. (See Fig. 6.)

#### SUMMARY

Drainage in thyroidectomy is unnecessary if a nonabsorbable technique is employed.

Careful hemostasis and special care for the remnant are responsible for the success of this method.

In our experience, cotton is highly satisfactory and makes undrained thyroid wounds possible.

By avoiding drainage, we have been able to reduce the average post-thyroidectomy hospital stay from sixteen to nine days, an economy for both hospital and patient.

# A NEW PLAN IN THE OPERATIVE TREATMENT OF PATIENTS WITH SEVERE HYPERTHYROIDISM

## THE USE OF SPINAL ANESTHESIA AS AN ADJUNCT TO THEIR PREOPERATIVE CARE

MAJOR CHARLES E. REA,\* MEDICAL CORPS, A.U.S.

IT IS the purpose of this communication to report briefly the employment of spinal anesthesia as an adjunct to the operative management of severe hyperthyroidism. This plan has been employed in twenty cases with real satisfaction. Whereas, the use of spinal anesthesia in the management of postoperative thyroid storm has been described previously from this clinic, and whereas Crile and Bartels, Stuart, and Johnson have employed spinal anesthesia for a similar purpose, the basis of the proposal described herein is predicated on the thesis that an effective spinal anesthesia, which would inhibit medullary adrenal releases during the operation, would help to forestall the occurrence of immediate severe postoperative reactions. It is not the intent to secure anesthesia to a level (second to fourth cervical segment) which would permit the operation being done under this agency alone. On the contrary, a somatic analgesia to about the fourth dorsal segment is derived with the use of spinal anesthesia, the analgesic for the performance of the operation upon the neck being obtained with the use of other agents—usually a combination of pentothal and cyclopropane.

### MODE OF MANAGEMENT

The usual considerations which have guided surgeons in the management of patients with severe hyperthyroidism constitute an integral part of the therapeutic program. Briefly the following are given careful notice:

1. *The Use of Lugol's Solution.*—Of all the components of preoperative treatment of patients with severe hyperthyroidism, there is none so abused as the use of Lugol solution. When iodine first came into general use in the early 1920's, the answer to the goiter problem was thought to be found. However, this has proved not to be the case in the ensuing years. Empirically, one gives five to ten drops of Lugol's solution three times daily to patients with hyperthyroidism. One should never give Lugol's solution for more than two-week periods without evaluating the clinical status of the patient. The practice of giving Lugol's solution for months to goiter patients is to be condemned, as it is not only unnecessary but also may confuse the clinical picture.

\*Formerly from the Department of Surgery, University of Minnesota Medical School, Minneapolis, Minn.

Received for publication, July 10, 1944.

The practice of treating children or adults with mild hyperthyroidism with small doses of iodine over a long period of time has been advocated by some clinicians. In our opinion this is a dangerous form of therapy for the reasons just mentioned, and it puts a big responsibility on the physician prescribing the treatment. Thyroidectomy is a safer and surer method of treatment. It is our policy to be more conservative with children developing mild degrees of hyperthyroidism about the time of puberty. Two instances of mild exophthalmic goiter in children have come to our attention, in which spontaneous remission of symptoms after puberty occurred. Older children with hyperthyroidism have been subjected to thyroidectomy similar to that in adults.

At this clinic Lugol's solution is given to patients with hyperplastic goiters and also to those with nodular goiters with hyperthyroidism, both pre- and postoperatively. In our experience it is not necessary to give iodine medication to patients with nodular goiter without hyperthyroidism, either before or after operation. Rather disturbing, however, is the fact that of 155 patients with "nontoxic adenoma of the thyroid" operated upon at the University of Minnesota Hospitals between 1933 and 1940, who had not received Lugol's solution preoperatively, three showed degrees of thyroid storm postoperatively. These were probably cases of latent hyperthyroidism, not diagnosed clinically. For this reason, it is my personal opinion that it does no harm to give the majority of patients with nontoxic adenomas of the thyroid Lugol's solution before operation. The question of what percentage of nodular goiters without hyperthyroidism will be made toxic by the use of iodine is important (so-called Jodbasedow). It is said that in Kocher's clinic the use of iodine for sterilizing the skin in goiter operations was forbidden. Kocher's successor, de Quervain, listed thirty-three cases of Jodbasedow in nine years. However, Dr. Carl Rice, at the goiter clinic at the University of Minnesota Hospitals, has purposely treated patients with nodular goiter without hyperthyroidism with low doses of Lugol's solution (one to two drops a day) up to a period of two years, and has not seen one who was made toxic by the iodine medication. Further, there are no statistical studies to show that there are more cases of toxic goiter developing among persons who took iodine for nodular goiter than among goitrous persons who did not take iodine (McClendon). It is my opinion that some instances of Jodbasedow are really cases of latent hyperthyroidism, flared up by stimuli other than the iodine. The whole question of Jodbasedow merits a complete and critical reinvestigation before definite conclusions are warranted, however.

2. *Mental and Physical Rest.*—By means of controlled environment and sedation, a state of mental and physical rest can be obtained in patients with hyperthyroidism. For sedation, phenobarbital, from  $\frac{1}{2}$  to 1 gr. three times a day, are used with seconal, from  $1\frac{1}{2}$  to 3 gr., at night. At this clinic the patients are allowed bathroom privileges.

The mental attitude of the patient toward his condition and the operation are very important because regardless of what the laboratory tests may show and how satisfactory his physical condition may seem, if the patient is nervous and apprehensive he is not a good candidate for operation.

3. *Diet*.—Patients with hyperthyroidism should be given a high caloric diet. A high protein and a high carbohydrate component should be stressed. The patient's weight is one of the best checks on how he is progressing. A patient with hyperthyroidism who is gaining weight, regardless of what the basal metabolic rate may be, shows that he is improving under therapy. We have checked plasma proteins of four patients with severe hyperthyroidism and have found them to be within normal ranges.

4. *The Use of Other Drugs*.—The reports to date concerning the use of thiouracil seem to indicate that that drug is of value in the pre-operative management of certain patients with hyperthyroidism. Thiamine chloride is given routinely to patients with hyperthyroidism at this clinic. Those whose clinical condition does not improve in spite of Lugol's solution (iodine-fast) are often improved by attention to rest, diet, sedation, or thiamine chloride. In six iodine-fast patients with goiter, the use of diiodotyrosine gave no more benefit than that obtained with Lugol's solution.

5. *Operation on Thyroid Gland*.—The following factors should be taken into consideration before operating on the thyroid gland: the patient's age, the size of the gland, the response to Lugol's solution, the duration of the hyperthyroidism, the basal metabolism rate, the pulse, the gain in weight, and the patient's general physical and mental condition. The procedure to be used should be decided in the surgeon's mind in the patient's room *before* operation and not at the operating table. If, from an evaluation of the patient's condition, just a ligation of the superior poles of the thyroid gland or a lobectomy is agreed upon, it is inviting disaster to proceed further just because the patient stood the stage procedure well. Moreover, if the patient begins to react badly while the surgeon is doing the procedure contemplated before operation, it is best to do the minimum and, if the operation has not gone too far, to close the wound as quickly as possible. The three fatalities that have occurred in this clinic during the past three years in thyroid patients (out of a total of 308 operations) have been due to failure to observe one or both of these two rules.

Since the whole rationale of thyroidectomy in hyperthyroidism is to shift the patient from a state of hyperthyroidism to one of hypothyroidism, hoping to hit a happy medium, one can realize how much the experience of the surgeon counts in judging how much of a thyroid should be removed. In severe thyrotoxic patients one aims to do a bilateral subtotal thyroidectomy in one or more stages. It is interesting to note how the stage procedure has passed from one of necessity



to one of election. At this clinic, a unilateral lobectomy has been the stage procedure of choice in the severely thyrotoxic patient. A right subtotal lobectomy is usually performed first, with surgical removal of the left side being deferred until two to four weeks later. The use of local, general inhalation or intravenous anesthesia, or combinations of these, depends somewhat on the choice and temperament of the surgeon. Ether is a bad anesthetic for thyrotoxic patients, as it tends to produce pulmonary edema. Cyclopropane has been used as the chief inhalation anesthetic at this clinic, but is contraindicated if the patient has cardiac irregularity. Its chief value lies in the high oxygen content of the mixture.

At the University Hospitals the use of intravenous pentothal ("sneak thyroidectomy") has proved of value in patients with toxic goiter. The procedure is as follows: For two or three days before operation the patient is given 1,000 c.c. of 5 per cent glucose in saline solution intravenously. Since operations are performed in the afternoon at this hospital, the patient is given a liquid breakfast on the day of operation and intravenous glucose solution. No other preparation is made, so that the patient is unaware that he is to be operated upon that day. Just before operation, when the infusion has just about been completed, intravenous pentothal is given through the same infusion needle. The sleeping patient is taken to the operating room where the neck is prepared for operation and inhalation anesthesia is initiated.

#### THE USE OF SPINAL ANESTHESIA IN PATIENTS WITH SEVERE HYPERTHYROIDISM

In spite of careful preparation and preoperative care, some patients with severe hyperthyroidism have had degrees of thyroid storm post-operatively. To prevent such an occurrence, spinal anesthesia in the operative management of severe hyperthyroidism has been used. This idea was suggested from the good results following the use of spinal anesthetic in a case of thyroid crisis. This case has been reported in detail elsewhere. To date, spinal anesthesia has been used for three patients with thyroid crisis with good results at this clinic.

Because of the good results following the use of spinal anesthesia in cases of thyroid crisis, it was suggested that spinal anesthesia might be used as a preoperative measure in cases of severe hyperthyroidism. A report of the first patient so treated is given in detail because when operation was first attempted, without the spinal anesthesia (control), the patient had a severe reaction on the table.

#### CASE REPORT

C. G., aged 41 years, was admitted to the University of Minnesota Hospitals, Oct. 11, 1941. He gave a history of dyspnea, and fatigability since the winter of 1940 to 1941. Rather marked irritability had been noted by his wife about eight months previously. He noticed a mass in his neck and pounding of the heart

approximately three months prior to admission. In spite of an increased appetite, he had lost thirty-five pounds in the past year. He had noticed tremor of the hands for approximately two years.

On admission, the patient's temperature was 98.8° F., pulse, 100, respiration 20, blood pressure 138/60.

Physical examination revealed a well-nourished, well-developed white man who was rather hyperactive. There was a mild exophthalmos of both eyes and the thyroid gland was diffusely enlarged and firm. No bruit was heard. The heart was of normal size and the tone was forceful; no murmurs were heard. The lungs were clear to auscultation and percussion and there were no abdominal masses. A fine tremor of both hands was present. There was a staring expression of the eyes and definite lid lag.

The patient had received Lugol's solution, ten drops three times a day, since Sept. 28, 1941. He had also been given phenobarbital, 1½ gr. three times a day, and thiamine chloride, 1 mg. four times a day. Some difficulty was experienced in raising his caloric intake sufficiently, but with a 5,200 caloric, high carbohydrate, high protein diet, his hunger was relieved and he began to gain weight. Basal metabolic rate, Sept. 18, 1941, was plus 84 per cent; Oct. 2, 1941, plus 74 per cent; and Oct. 12, 1941, plus 51 per cent. The basal metabolic rate never went below this level at any subsequent test. His pulse rate was not excessive and consequently it was thought that lobectomy should be attempted.

Oct. 28, 1941, pentothal was given intravenously in his room and he was taken asleep to the operating room, where inhalation cyclopropane anesthesia was instituted. At the beginning of the operation the blood pressure was 140/80 and the pulse 120 per minute. After making the skin incision in the neck, his blood pressure was 180/90, but the pulse was still 120 per minute. On cutting through the platysma muscle and retracting the strap muscles of the neck, the blood pressure was found to be 220/100 and the pulse 160. Some of this untoward reaction was thought to be due to the cyclopropane, so this anesthetic was discontinued and only oxygen given. However, since the patient did not improve, the skin incision was closed and the patient transferred back to his room.

The patient had quite a stormy time for the first few postoperative days. Because of this reaction, it was decided to give him a course of deep x-ray therapy to the thyroid gland; he received 500 r/air to the anterior thyroid region and 250 r/air to the right and left lateral thyroid areas over a period of nine days from Nov. 5 to 14, 1941. His basal metabolic rate Nov. 7, 1941, was plus 53 per cent. The patient became somewhat restless and did not seem to acquire a mental and physical calmness during this time. November 17, 1941, the patient was operated upon again. Anesthesia was induced with intravenous pentothal sodium in his room. In the operating room 75 mg. of procaine hydrochloride was given intraspinally in the third lumbar interspace. Anesthesia, as determined by pinching the skin with a Backhaus forceps, was obtained to the third intercostal space. Inhalation ethylene anesthesia was then given and a bilateral subtotal thyroidectomy performed.

The patient had a surprisingly smooth operative course. The blood pressure was maintained at about 140/80 and the pulse between 100 and 120. Postoperatively, his condition was good and, except for a hematoma in the wound, his course was uneventful. He was discharged, Nov. 30, 1941, with instructions to report for checkup to the outpatient clinic. When seen Jan. 16, 1942, his basal metabolic rate was plus 35 per cent, his weight was 215 pounds, and he looked and felt well. April 16, 1942, his basal metabolic rate was plus 12 per cent, his weight 220 pounds, and he was doing moderately heavy work.

To date, we have operated upon twenty patients with severe hyperthyroidism, using a combination of intravenous pentothal, spinal and

inhalation anesthesia. Under this regimen we have been able to do bilateral subtotal thyroidectomy upon patients who heretofore we would have done only stage procedures. In eight of the patients the basal metabolic rate was never lower than plus 60 per cent before operation. (See Table I.) We have been impressed with the smooth operative and postoperative course in these cases.

The whole purpose of the spinal anesthesia as used in these cases is to inhibit medullary adrenal releases during the operation, which would forestall the occurrence of an immediate severe postoperative reaction. It is not the intent to secure anesthesia to a level (second to fourth cervical segment) which would permit the operation being done under this agency alone. The question comes up, of course, how do we know that the adrenals are so important in thyroid storm. We believe that the adrenals are important, first because of the reactions accompanying the so-called Goetsch test. In this test, if adrenalin is given intravenously to patients with mild or latent hyperthyroidism the patient gets a reaction akin to a thyroid storm. Second, if there were signs of hyperadrenalin, one would expect an increase in the blood sugar. We have examined the blood sugar of these patients before, during, and after thyroidectomy using spinal anesthesia, and have found that the blood sugar is not increased. The short-time factor in performing the operation must be taken into consideration in evaluating these normal levels. No determinations of the amount of adrenalin in the blood during these operations have been made as there is no accurate method known to date.

It is important that a somatic analgesia to about the fourth dorsal segment be derived from the use of spinal anesthesia, if one hopes to inhibit the splanchnic nerves to the adrenal glands. We have checked the level of spinal anesthesia by noticing when the patient gives evidence of pain by pinching the skin of the chest at different levels before induction with general anesthesia and after operation when the patient is arousing from the anesthetic.

Procaine has been used as a spinal anesthetic, the dose varying from 80 to 120 mg. The head of the table may be tilted downward 10 degrees for a few minutes to assure high enough anesthesia. In so doing, the patient's head should be raised on a pillow to prevent the anesthesia from extending to the cervical segments.

In these cases we have not used any pressor drugs to prevent or treat falling pressure. In two instances the blood pressure fell rather alarmingly during operation. This was treated by Trendelenburg position and intravenous fluid.

It is to be emphasized that it is not necessary to use a spinal anesthetic in all thyrotoxic cases. However, for our experience, its use in the operative treatment of certain cases of severe hyperthyroidism would seem justified and the risk seems less than it would be if one attempted to do the same operation without the spinal anesthetic.

PA- TIENT	HOS- PITAL NO.	AGE (YR.)	SEX	CLINICAL DIAGNOSIS	DURA- TION OF SYMPT- OMS	OF PRE- OPERA- TIVE TREAT- MENT	OPERATION	PATIENT'S CONDITION		B.M.R. (%)	PULSE	WEIGHT (LB.)
								DURING OPERA- TION	AFTER OPERA- TION			
E. M.	702469	27	F	Diffuse hyper- plastic goiter	3 yr.	2 to 3 weeks	Bilateral subtotal thyroidectomy	Good	Good; little rise in blood pressure	(A) +68 +19 (B) --- (C) + 5 3 mo. P.O.	(A) 70 (B) 100 (C) 84	(A) 189 (B) 188 (C) 197½ 3 mo. P.O.
O. K.	728088	32	F	Diffuse hyper- plastic goiter	3 mo.	2 weeks	Bilateral subtotal thyroidectomy	Good	Good	(A) +81 +70 +34 (B) --- (C) -10 6 wk. P.O.	(A) 80 (B) 110 (C) 80	(A) 130 (B) 132 (C) 154 6 wk. P.O.
H. S.	728201	27	F	Diffuse hyper- plastic goiter	4 mo.	2 weeks	Bilateral subtotal thyroidectomy	Good	Good	(A) +73 +57 (B) --- (C) -11	(A) 90 (B) 120 (C) 100	(A) 140 (B) 140 (C) 155 6 wk. P.O.
E. P.	733570	30	F	Diffuse hyper- plastic goiter	3 yr.	10 days in hos- pital	Bilateral subtotal thyroidectomy	Good	Good	(A) +70 +48 (B) --- (C) + 7	(A) 85 (B) 90 (C) 80	(A) 146 (B) 144 (C) 161½ 9 wk. P.O.
E. L.	736110	20	M	Diffuse hyper- plastic goiter	3 mo.	15 days	Bilateral subtotal thyroidectomy	Good	Good	(A) +64 +32 (B) --- (C) Not done; too recent	(A) 100 (B) 90 (C) 90	(A) 120 (B) 122 (C) 124 1 week
A. T.	736034	32	F	Diffuse hyper- plastic goiter	9½ mo.	21 days	Bilateral subtotal thyroidectomy	Fair	Good	(A) +92 +51 (B) --- (C) Not done; too recent	(A) 110 (B) 90 (C) 100	(A) 119 (B) 120 (C) 134½ 4 wk. P.O.
S. D.	717339	36	F	Diffuse hyper- plastic goiter	7 mo.	2 weeks	Bilateral subtotal thyroidectomy	Good	Good	(A) +62 +62 (B) --- (C) +34	(A) 110 (B) 100 (C) 90	(A) 102 (B) 104 (C) 110 2 wk. P.O.

## SUMMARY

We have been impressed with the use of spinal anesthesia as an adjunct to the operative and postoperative management of severe hyperthyroidism. The basis of the proposal is predicated on the thesis that an effective spinal anesthesia, which would inhibit medullary adrenal releases during the operation, would help to forestall the occurrence of immediate severe postoperative reactions. It is not the intent to secure anesthesia to a level (second to fourth cervical segment) which would permit the operation being done under this agency alone. On the contrary, a somatic analgesia to about the fourth dorsal segment is derived with the use of spinal anesthesia, the analgesic for the performance of the operation upon the neck being obtained with the use of other agents, usually a combination of pentothal and cyclopropane. The idea is rational and feasible; further investigation is necessary to determine how valid the premises are.

## REFERENCES

1. Bartels, E. C., Stuart, C. K., and Johnson, E. C.: The Adrenal Gland in Hyperthyroidism, *Tr. Am. A. Study Goiter*, p. 133, 1940.
2. Crile, G., Jr.: Management of the Patient With Hyperthyroidism: Preoperative and Postoperative Care, *S. Clin. North America* 16: 1051, 1936.
3. Fiske, F. A.: Thyroid Crisis as a Postoperative Complication, *Tr. Am. Therap. Soc.*, p. 133, 1939-1940.
4. Foss, H. L., Hunt, H. F., and McMillan, R. M.: The Pathogenesis of Crisis and Death in Hyperthyroidism, *J. A. M. A.* 113: 1090, 1939.
5. McClendon, J. F.: Iodine and the Incidence of Goiter, Minneapolis, 1939, University of Minnesota Press, pp. 95-96.
6. McGregor, J. K.: Hyperthyroid Crisis, *West. J. Surg.* 49: 367, 1941.
7. Maddock, W. G., Collier, F. A., and Pedersen, S.: Thyroid Crisis: Its Relation to Liver Function and Adrenalin, *Tr. Am. A. Study Goiter*, p. 61, 1936.
8. Pemberton, J. de J.: Reactions Following Operation for Hyperthyroidism, *Ann. Surg.* 104: 507, 1936.
9. Rea, C. E.: Some Problems in the Pre- and Postoperative Care of Patients With Hyperthyroidism, *Minnesota Med.* 26: 570-576, 1943.
10. Rea, C. E.: Unsolved Problems in Hyperthyroidism, *J. Tennessee M. A.* 37: 10-14, 1944.
11. Werner, A. A.: *Endocrinology, Clinical Application and Treatment*, Philadelphia, 1937, Lea & Febiger, p. 491.

## THE MANAGEMENT OF POSTOPERATIVE COMPLICATIONS IN THYROID SURGERY

HOWARD M. CLUTE, M.D.,\* FRANCIS R. KENNEY, M.D., AND  
BURTON E. HAMILTON, M.D.,† BOSTON, MASS.

THE early detection and proper management of postoperative complications are an essential part in the care of all surgical cases. In surgery of the thyroid gland, however, immediate and personal attention to postoperative care is not only desirable, but frequently is life-saving. In few other fields of surgery may the postoperative troubles of the patient so quickly produce dire results. It is important, then, in any discussion of thyroid surgery that due attention be paid to postoperative care.

As has been so frequently observed, a set team of anesthetist, surgeon, assistant, and nurse is of the greatest value in thyroid surgery and in postoperative care. The less frequently the personnel of this team is changed the more smoothly and efficiently do they work. In our clinic, the anesthetist accompanies each thyroid patient back to the room and sees the patient safely into bed. She makes certain that the patient's airways are free. If there is any doubt about this, she remains with the patient until breathing is comfortable and easy. Oxygen is given many patients for some hours after operation, especially if they are toxic, and this is started and checked by the anesthetist. Either a tent or an intranasal catheter has proved most satisfactory in our hands. Most patients find the B.L.B. mask unpleasant to wear.

Intravenous fluid is also ordered and frequently given by the anesthetist immediately on the patient's return to bed. This may be glucose in water or glucose in saline solution, with or without Lugol's solution added, as the situation demands.

On return to bed the patient is placed flat or on one side for the first six or ten hours. Then the head of the bed is gradually raised and a sitting position assumed and maintained for most of the immediate postoperative period.

Nausea and vomiting<sup>2, 3</sup> are not infrequent annoyances in the first twelve to twenty-four hours after goiter surgery. Usually due to the preoperative and postoperative medication and the anesthesia, they are readily managed by replacing intravenously the fluids and salts that have been lost. Not infrequently we find that the nausea and vomiting seem to be related to injections of morphine and cease when this

\*Professor of Surgery, Boston University School of Medicine; Surgeon in Chief, Massachusetts Memorial Hospitals; Surgeon, New England Baptist Hospital.

†Cardiologist, Boston Lying-In Hospital, and New England Deaconess Hospital.  
Received for publication, July 10, 1944.

drug is discontinued. Very often at the end of the first postoperative day codeine and aspirin are substituted for morphine and effectively control discomfort. Except in the rare cases of vomiting due to a postoperative storm, this complication has never been a serious problem.

Postoperative hemorrhage<sup>2, 3, 6, 10, 11</sup> is a very rare occurrence today in thyroid surgery, but when it occurs immediate and active treatment is essential. No serious hemorrhage has occurred in our practice for many years, due, we believe, to our constant attention to all oozing in the field at operation and our tendency to tie both the superior and inferior thyroid arteries in each case in which oozing is troublesome.

Hemorrhage, when it does occur, may develop at catastrophic speed. Usually patients having a serious thyroid hemorrhage suffer more from the resulting pressure of the blood on the trachea than they do from acute blood loss. A patient perfectly comfortable one moment may suddenly develop a wide swelling across the neck which bulges forward almost obliterating the normal submental depression. With this swelling there is increasing stridor and anxiety, and very little time for delay. The skin clips must be removed in the room and the sutures holding the prethyroid muscles cut. This releases the tracheal pressure and overcomes the stridor. Large gauze packs are placed over the wound and the patient is quickly transported to the operating theater for control of the bleeding.

In our experience a severe hemorrhage of this type has always been from the superior or inferior thyroid artery. It has been disconcerting in some of these cases to find no artery pumping when the field was exposed. After careful exploration, however, the vessel usually starts bleeding again and the main trunk can be tied. When no one vessel can be found in such a case, it is best to ligate both superior and inferior thyroid arteries before sending the patient back to bed.

Occasionally a hematoma<sup>7</sup> will appear under the skin flap three or four days postoperatively, the wound having been normal up to this time. No interference with breathing is present. We usually find that this is due to oozing from a small vein under the skin flap. The postoperative course will be shorter and smoother and the scar probably better if this hematoma is evacuated in the operating room and the skin edges reapproximated. Frequently one dislikes subjecting the patient to a second operation and, therefore, waits for the hematoma to liquefy and drain externally. This requires many dressings, but usually the results are good.

For two years or more, we have removed all the skin clips in the thyroid incision twenty-four hours after the operation. This, we believe, has greatly improved the scars. No wounds have separated and no trouble has occurred due to this procedure.

In past years it has been our experience that 85 per cent or more of all our thyroid incisions showed a collection of serum<sup>2, 6</sup> under the skin

flap during the postoperative course. By probing with a small needle this was released with little serious effect on the scar. In recent years, however, serum has been extremely uncommon in these wounds and, in fact, rarely occurs unless a hematoma has been present. This change, we believe, is due to our use of 4-0 catgut for ties in the skin flap, fine catgut in the deep ties, and our technique of retracting rather than cutting the prethyroid muscles in most cases. Less trauma and less catgut have given markedly improved wounds.

Sometimes in large goiters there is a brawny edema<sup>2</sup> extending across the neck for several days postoperatively. This generally clears up in a few days. Any accompanying discomfort is alleviated by hot poultices or ice bags. Very rarely infection<sup>2, 3, 6</sup> occurs under the skin flap. This has never been dangerous. It is treated with hot flaxseed poultices and probing for any purulent fluid in the wound. Anesthesia of the skin flap<sup>2</sup> may persist for some time, but is usually gone at the end of six months.

Very rarely in extremely toxic patients there may be jaundice, probably due to accentuation of the liver damage<sup>7, 10</sup> occurring in severe hyperthyroidism. A high carbohydrate, high protein diet should be given in these cases as well as generous amounts of intravenous glucose.

Infection extending into the superior mediastinum<sup>2, 3, 10</sup> may occur after thyroid surgery, but certainly this is one of the rarest complications in our experience. It is most to be feared following the removal of a deeply substernal goiter. It should be suspected if there are a rising pulse and a moderate fever, the pulse usually being proportionately much higher than the fever or toxicity of the patient. X-ray pictures should show typical widening of the mediastinum. Immediate reoperation to cut transversely the prethyroid muscles and drain the mediastinum is indicated. The prognosis is bad unless the fluid released is the result of inadequate drainage of the substernal area and is relatively sterile. Chemotherapy is used in these cases and may be helpful.

Some degree of tracheal irritation and tracheitis<sup>2, 3, 10, 11</sup> is very common after thyroidectomy. We believe that the degree of tracheitis is in most cases directly proportional to the roughness of the surgery. Rough handling of the larynx and trachea, especially on the posterior surfaces, seems to us to produce marked tracheitis. Certainly the dissection of the thyroid from the front of the trachea causes little difficulty. Mild degrees of tracheitis disappear in from twenty-four to forty-eight hours without special treatment. In some instances a steam kettle in the room seems to make breathing more comfortable.

Marked stridor, cough, trouble in swallowing, and even regurgitation of liquids through the mouth or nose occasionally occur in postoperative goiter cases. These are most unusual, and it is probably true in such cases that there has been an injury to: (1) either the superior or inferior laryngeal nerve, (2) the fine muscles of the larynx or, possibly, as Cole<sup>5</sup>



has suggested, (3) an actual spasm of the tracheal muscles. Temporary relief in these patients may be gained by using oxygen, or oxygen and helium inhalations. If marked swelling is present in the wound it must at once be widely opened and preparations made for tracheotomy.

The surgeon's great tendency in the presence of marked stridor is to delay tracheotomy too long. Men still say that "when cyanosis appears, a tracheotomy must be done." This policy of waiting for cyanosis before doing a tracheotomy will result in some fatalities because the margin of safety in partial tracheal obstruction is very low and any slight increase in the obstruction may at once produce a fatality. We have done tracheotomies in such cases, being gratified by the immediate relief obtained and astonished at the failure of the procedure to leave an unsightly scar.

Certainly we are convinced that marked tracheal obstruction with severe stridor can occur without any injury to the recurrent laryngeal nerves. We have seen both vocal cords functioning well, and normally five days after a tracheotomy had been necessary for tracheal and laryngeal spasm with obstruction.

Injury to one recurrent laryngeal nerve<sup>2, 6, 8</sup> may occur during thyroidectomy with no accompanying symptoms. After the operation the patient's voice may be affected, particularly as to the tone and volume. In many instances the voice returns very nearly to normal, but in others a permanent change is apparent. Injury to one recurrent laryngeal nerve is, in our experience, very rare and never fatal. No special treatment is indicated.

Injury to both recurrent laryngeal nerves is a most serious matter, carrying in its train marked or even fatal postoperative complications. Bilateral injury to the recurrent nerves should be prevented at any cost. In over 5,000 goiter operations performed by one of us (H. M. C.) this has never occurred.

Bilateral vocal cord paralysis may cause immediate and serious laryngeal obstruction with obvious inspiratory stridor. Examination of the larynx makes the diagnosis readily apparent. If the obstruction is pronounced, immediate tracheotomy must be done. In many cases the seriousness of this complication is not apparent until the patient is up and about. With increased exercise, breathing becomes much more difficult and a great increase in stridor occurs.

In these cases it is wise to postpone any radical treatment of the paralyzed cords for eight or ten months or more. Occasionally, one of the cords will regain its motility and the breathing will thereby improve. If, after such a delay, there is still complete bilateral cord paralysis, radical operation for its improvement may be advised.

Hoover<sup>8</sup> has had good results with bilateral submucous resection of the cords in these cases. More recently King<sup>9</sup> has reported good results

from transplanting the omohyoid muscle to the base of one arytenoid cartilage and reconstructing the larynx, thus enlarging the glottic fissure.

Postoperative thyroid storms<sup>2, 10, 11</sup> are today far less frequent and much less severe than in the past. With the increasing care and greater length of the preoperative preparation of thyrotoxic patients and careful adjustment of the stages of operation to each individual, serious thyroid storms can be avoided. From our experience to date with thiouracil,<sup>12, 13</sup> we believe that the few serious reactions we now see after thyroidectomy can probably be avoided.

In recent years the occasional serious reactions after thyroid operations have manifested themselves largely by an undue increase in the pulse rate and a rise in temperature. Formerly these symptoms were commonly accompanied by nausea and vomiting, often very persistent. Rarely today do we see the great muscular activity and mental and emotional excitement that were so frequent in the early days of thyroid surgery. Perhaps this is due to the improved preoperative preparation.

In serious postoperative thyrotoxic cases we place the patient in an oxygen tent at once and continue this for hours or days as is indicated by the patient's reactions. Intravenous instillations of 5 per cent glucose in normal saline solution alternated with 5 per cent glucose in distilled water are given so that the urinary output is brought to 1,000 or 1,500 c.c. per day. Ten minims of Lugol's solution are added to each intravenous infusion until 30 minims per twenty-four hours have been given. Morphine is given in sufficient doses so that the patient rests quietly.

Careful attention must be paid to the lungs in these cases and chemotherapy with the appropriate sulfonamide drug started at once if any suggestion of pneumonia is present.

Following surgery (whether this is directed at the thyroid gland or elsewhere), patients with hyperthyroidism tend to show evidence of increased load on the circulation. The pulse rate quickens and the blood pressure sometimes rises. The systolic pressure rises proportionately more than the diastolic pressure. There are accompanying evidences of hurried circulation. Although there is much individual variation, the average curve of the load on the circulation appears to rise slowly during the first twenty-four hours, then rise abruptly. Then, during the thirty-six to forty-eight hours following the operation there is, typically, a rapid lessening of the load toward normal. In some, the return toward normal is delayed for several days even though there are no apparent complications. During this period when the circulatory load appears to be high, other symptoms of increased hyperthyroidism may appear.

Congestive heart failure rarely appears *for the first time* following operation, although in patients who have had heart failure previously and in the rarer cases in which the patients have to be operated upon

while actually in congestive heart failure, signs of failure may reappear or be somewhat aggravated. Elderly patients and those with other complicating heart conditions should have special care, to spare the heart unnecessary strains. They must have adequate rest, sedation, nursing care, and oxygen, if needed, and in particular they must have their fluid administration carefully controlled so that there is an adequate supply but not an excess. It is easy to overcrowd the circulation and produce signs of congestive heart failure by heedless forcing of fluids to old people or those with a cardiac condition. It sometimes produces violent attacks of paroxysmal dyspnea. For such thyrocardiacs or potential thyrocardiacs, it should be a rule to visit each one frequently, and always before any large amount of fluid is given; routine orders for fluid administration must not be relied upon. A nurse should stand by the patient while intravenous fluid is given, with instructions to stop the administration instantly if respiratory distress or quickened breathing appears.

As is commonly known, hyperthyroidism tends to cause *auricular fibrillation*. It is a "law" that if hyperthyroidism causes auricular fibrillation, when the hyperthyroidism is adequately treated the auricular fibrillation will disappear. Therefore, many patients who have auricular fibrillation when first seen return to normal rhythm when the hyperthyroidism is treated. No treatment directed at the auricular fibrillation is needed except control of the rate by digitalis. A long time should be allowed to go by following surgery before special medication other than digitalis is indicated in an attempt to restore normal rhythm.

Patients who have normal heart rhythm when operated upon frequently develop auricular fibrillation during the postoperative period when the load on the circulation is high. Those who have had transient attacks of auricular fibrillation before operation are most likely to develop it during the critical postoperative period. Among those who have not had it previously, it rarely appears postoperatively in patients under 40 years of age. It appears more and more often as age advances. The severity of the hyperthyroidism and the postoperative reaction are also factors.

The appearance of auricular fibrillation in a patient following thyroid surgery is not cause for alarm. Nor does it indicate drastic therapeutic efforts. It does indicate watchfulness, close attention to the patient's wants and comfort, and thoughtful treatment with digitalis or drugs with similar action. For years we have used digitalis in the control of the rate in auricular fibrillation in hyperthyroidism with gratifying effect. Our rules for its use are as follows: We do not use digitalis in patients who have normal rhythm. Rare exceptions to this rule would be (1) patients with complicating serious heart disease, and we sometimes digitalize carefully (2) patients who have had re-

peated attacks of transient auricular fibrillation, since they are almost certain to have a return of the auricular fibrillation postoperatively, and we can anticipate this comfortably by leisurely digitalization in preparation for operation.

Some variations in the strength of digitalis preparation are to be expected, and some variation in the tolerance of individuals to the drug. Slight over digitalization, if not long-continued or severe, is usually not actually dangerous. But it can cause distressing and even serious symptoms. At best, it is uncomfortable for the patient.

Until recently, we have given from one-half to two-thirds of the estimated full dosage at the first dose, and then three-grain or one and one-half grain doses every eight hours until the heart rate is satisfactorily controlled or until toxic symptoms appear. We then maintain the action by suitable daily doses under supervision.

This plan has worked well, but by this method there is usually a delay of many hours before the patient's circulation has received the full benefit of the drug action. Recently we have used a preparation of Lanatoside C, intravenously. We have used for the initial dose approximately 6.5 cat units. There may be a prompt and appreciable response. On several occasions normal rhythm has appeared within less than one-half hour after the first intravenous dose, but often considerably more has been needed, either intravenously or by mouth or rectum, before the pulse rate has been satisfactorily controlled. We are still learning about the amount and timing of the dosages, and therefore do not recommend any fixed procedure. But we believe that the intravenous use of Lanatoside C is a distinct advance in the treatment of auricular fibrillation when it first appears, and when the patient has not had digitalis within two weeks.

Auricular flutter occasionally occurs postoperatively and is regarded and treated like auricular fibrillation. Other paroxysmal tachycardias are no more likely to occur after thyroid than after other operations.

Since hyperthyroidism and myxedema rarely if ever appear as immediate postoperative complications in thyroid cases, they are not discussed in this paper.

Tetany<sup>2, 6, 7, 10, 11</sup> occurs after thyroid surgery if the blood supply of the parathyroids is partly destroyed or if a sufficient number of parathyroid glands are removed to reduce markedly their secretion. Postoperative tetany is rare and is usually transient. We have seen one transient case in our last 1,000 thyroidectomies.

Tetany may be suspected if typical carpopedal spasms and other muscular contractions occur hours or days after a thyroidectomy. Trousseau's and Chvostek's signs when positive make the diagnosis quite certain. Examination of the blood calcium will show it to be low. Occasionally postoperative tetany will have a sudden onset and the patient will have such muscular spasms that breathing and swallowing

are rapidly and seriously affected. Here there is no time for blood calcium studies. Active measures must be undertaken at once.

In such acute cases from 5 to 10 c.c. of 10 per cent calcium chloride should be given at once intravenously, mixed with 100 c.c. of normal saline solution to prevent sloughing. This is effective in a matter of minutes and controls the acute spasms. Calcium lactate, from 2.5 to 4 Gm. dissolved in hot water, every two to four hours along with two to three teaspoons of cod-liver oil daily assists the calcium metabolism. Calcium lactate, being less irritant, is sometimes given intravenously instead of calcium chloride and requires no saline solution for dilution. Occasionally parathormone extract subcutaneously may be used. Pemberton and Stalker<sup>11</sup> feel that A.T.10 with calcium lactate may be the easiest way to treat chronic parathyroid deficiency. All such therapy must be carefully followed and repeated blood calcium studies made.

Severe ocular complications<sup>10</sup> may follow thyroid surgery in patients having marked exophthalmos. These may be due to injury to the cornea during the adjustment of the anesthetist's mask, or other types of trauma and infection in eyes left unprotected by incomplete closure of lids. Such eye complications should be seen and treated at once by an ophthalmologist. The thyroid surgeon and his team must be particularly careful before, during, and after operation, in the care of the eyes of the patients who have pronounced exophthalmos.

The scar<sup>2</sup> after a successful thyroidectomy is usually the only reminder that the patient has of her previous illness. In a few months all the symptoms that made thyroid surgery necessary will be forgotten, but the scar, especially if it is a bad one, will remain and will receive much attention; hence we lay great stress on the proper placing of the thyroid incision at operation and its care afterward. As previously stated, we remove all the clips twenty-four hours after the operation; superficial drains are removed with the clips; if serum or blood collects under the skin flap it is immediately released by use of a very fine probe. When the wound is healed there may be adherence between the scar and the fascia which causes an unsightly irregularity. This can be improved greatly by gentle massaging to lengthen the adhesion. We start this ten or twelve days after operation. Deep induration and swelling may be present for five or six weeks in some cases, especially if the muscles have been cut. No treatment for this other than reassurance is needed.

It is apparent that with adequate preoperative preparation of the toxic thyroid patient the most serious complication of thyroid surgery, postoperative storm, will be absent or mild. It is equally true that with increased technical skill the difficulties due to injury of recurrent laryngeal nerves or to parathyroid glands can be avoided. Today the complications after thyroidectomy are chiefly those common to any operation, and like all surgical complications can be largely avoided by careful preparation for operation and a skillful operative technique.

## REFERENCES

1. Beilby, G. E.: The Treatment of Complications of Thyroid Surgery, New York State J. Med. 41: 2310-12, 1941.
2. Clute, H. M.: The Treatment of the Complications Arising After Operations on the Thyroid Gland, Boston M. & S. J. 191: 1147, 1924.
3. Clute, H. M.: Complications Subsequent to Thyroidectomy, S. Clin. North America 4: 1475, 1924.
4. Clute, H. M., and Williams, R. H.: Thiouracil in Preparation of Thyrotoxic Patients for Surgery, Ann. Surg. (In press.)
5. Cole, W. H.: Laryngeal Spasm and So-called Tracheal Collapse, Arch Surg. 39: 10-27, 1939.
6. Crile, G., Jr.: The Management of Complications During and Following Thyroidectomy, S. Clin. North America 21: 1291-1301, 1941.
7. Dinsmore, R. S.: Prevention of Thyroid Complications, Lahey Birthday Vol., pp. 145-152, 1940.
8. Hoover, W. B.: Paralysis of the Recurrent Laryngeal Nerve as a Complication of Thyroid Surgery, Lahey Birthday Vol., pp. 223-230, 1940.
9. King, B. T.: A New and Function-Restoring Operation for Bilateral Abductor Cord Paralysis, J. A. M. A. 112: 814-823, 1939.
10. Mayo, C. W., and Miller, J. M.: The Thyroid Patient: Pre- and Postoperative Care in Relation to Thyroid Operations, Am. J. Nursing 40: 771-778, 1940.
11. Pemberton, J. deJ., and Stalker, L. K.: Preoperative and Postoperative Care of the Patient With Hyperthyroidism, S. Clin. North America 20: 941-952, 1940.
12. Williams, R. H., and Bissell, G. W.: Thiouracil in the Treatment of Thyrotoxicosis, New England J. Med. 229: 97-108, 1943.
13. Williams, R. H., and Clute, H. M.: Thiouracil in Thyrotoxicosis: Treatment of 72 Cases, New England J. Med. 230: 657-667, 1944.

## THE PROBLEM OF THYROID CRISIS\*

ROBERT W. BUXTON, M.D., ANN ARBOR, MICH.

*(From the Department of Surgery, University of Michigan Hospital)*

**D**ESPITE the great progress made in the last several decades in the recognition, treatment, and pre- and postoperative care of patients with diseases of the thyroid gland, there is still that group of patients who suddenly and unexplainedly, during the course of their disease, showed a profound and severe reaction designated as thyroid crisis. This interlude in the course of an apparently well-known disease is the cause of much speculation and the source of much medical comment.

As in all diseases resulting from a malfunctioning of the glands of internal secretion, there are all degrees of apparent dysfunction of the thyroid gland. Those patients exhibiting a marked disturbance of the central nervous system with overwhelming changes in the heat-regulating mechanism and accentuation of all of the symptoms of thyrotoxicosis are adjudged in thyroid crisis. To many clinicians any sudden pre- or postoperative variation in this direction is termed crisis, while to others only those patients who progress and terminate fatally fall into this group.

A wide clinical, pathologic, and physiologic search of the nervous system, the cardiovascular system, the liver, thymus, and adrenals, along with the physicochemical analysis of certain elements in the circulating body fluids in these patients has failed, to date, to shed any clear light upon a single factor to which the etiology of thyroid crisis can be solely attributed. Much of the recent experimental work has been carried out on this problem, and many of the clinical manifestations of the patient in crisis reproduced and an explanation tendered.

In an overall survey of the frequently reported cases, two outstanding clinical features appear common to all: (1) There is a progressive augmentation of all of the symptoms of thyrotoxicosis as it pertains to each of the great body systems (central nervous system, cardiovascular system, and hepatorenal system) until recovery or death ensues. (2) The terminal clinical signs and symptoms and the necropsy findings emphasize a breakdown in one or more of these systems. There is no uniformity of findings and no pathognomonic features common to all cases.

It is our impression that thyrotoxicosis is not a fatal disease when correctly treated, that thyroid crisis is not a specific entity, and that death in this state results from the various complications associated with the augmented metabolism which are often injudiciously and inaccurately treated.

\*Aided by The James and Elizabeth Inglis Fund for Surgical Research.  
Received for publication, July 10, 1944.

The deaths in thyroid crisis are frequently "cardiac deaths," at least terminally, and this aspect has received universal attention. There are at least three opinions concerning the effects of thyroid disease on the heart,<sup>1</sup> namely, (1) that thyrotoxicosis has no effect upon the heart except to increase the metabolic activity, (2) that the thyroid disease causes myocardial damage, hypertrophy of the heart, and various clinical cardiac manifestations, and (3) that thyrotoxicosis acts only as a catalytic agent and brings to the surface latent cardiovascular lesions.

The work of Raab<sup>2</sup> and of others suggests, as a fourth alternative, that increased production of epinephrine-like substances may produce the myocardial hypertrophy and dilatation, the arrhythmias and the myocardial degeneration in patients with thyrotoxicosis. He has found abnormally high concentrations of "epinephrine-like catechols" or of epinephrine proper and sympathin in the hearts of the majority of a selected group of patients who died from cardiac failure. Certain hormonal and nutritional factors were found to enhance the accumulation of the epinephrine-like catechols in the hearts of experimental animals. Two of these factors which qualitatively increased this desired accumulation were an overdose of thyroxin and a vitamin B<sub>1</sub> deficiency. The fundamental role of sympathomimetic amines with a catechol nucleus in the generation of myocardial disease is further stressed by an abundance of observations regarding the experimental production of the characteristics of myocardial disease (arrhythmia, anoxic changes in the electrocardiogram, anginal pain, pulmonary edema, hypertrophy and dilatation of the heart, myocardial degeneration and necrosis, cardiac failure and death) through the administration of epinephrine and related amines.

Crile<sup>3</sup> has pointed out that the known precipitating factors of thyroid disease (fear, anger, worry, infections, operations, pain, asphyxia, hemorrhage, and physical exertion) are factors stimulating the adrenals.

With some of these facts in mind Maddock and associates<sup>4</sup> studied the concentration of epinephrine-like substances in the blood of patients with hyperthyroidism. No evidence was found of this substance in the peripheral venous blood of the majority of the patients who were responding well to the routine preoperative treatment. In patients whose progress was not satisfactory and in whom fever was present, the test occasionally showed the presence of a small amount of epinephrine-like substance. A few patients postoperatively showed a positive test, the highest values being obtained in two patients of the group tested who developed severe thyroid crisis. In one of these, the patient who recovered, the epinephrine test became negative about the time the crisis subsided.

After correlation of these facts and findings, one may assume that the clinical cardiac findings and the cardiac deaths resulting in thyrotoxicosis and thyroid crisis follow excessive concentration of the sympha-



thomimetic amines in cardiac muscle. The effect of the sympathomimetic amines upon the oxygen uptake in cardiac muscle and therefore the effect of diminished oxygen pressures or anoxia is not well known.

Perhaps the most outstanding features, and certainly the most striking in thyroid crisis, are those of the central nervous system. They are in general the symptoms produced by an anoxic anoxia. In milder cases of thyroid crisis, patients have the general features of "mountain sickness," a feeling of well-being, exhilaration, talkativeness, emotional outbursts (such as laughing and crying), quarrelsomeness, and development of fixed ideas. The symptoms of fulminating crisis are those of a severe, acute oxygen deprivation, namely, delirium, mania, hyperpyrexia, and coma.

Since Magnus-Levy, in 1896, suggested that the thyroid hormone might act either directly on tissues or indirectly by way of the nervous system, numerous attempts have been made to locate its site and manner of action. An outstanding contribution to this problem was made by Cohen and Gerard<sup>6</sup> in 1937. These workers and others have shown in experimental animals that the respiration of individual cells is enhanced by thyroid hormonal action, for an increased oxygen consumption by hyperthyroid tissues persists *in vitro*. The oxygen consumption of hyperthyroid brains is approximately four times as much as that of normal brains on adding substrates which are involved in carbohydrate oxidation and glycolysis. Analysis of the respiration changes, induced by accelerators, methylene blue and cresyl blue, and such inhibitors as cyanide, malonate, iodoacetate, arsenite, barbital, and urethane, indicates that the absolute concentration of various enzyme systems is greater in hyperthyroid than in normal brain and that certain dehydrogenases are increased relatively more than oxidases. This work has been further investigated by Kessler and Gellhorn,<sup>7</sup> who found the sensitivity of unanesthetized animals to lowered oxygen pressure was greatly accentuated following the administration of thyroid powder. The electroencephalogram was the method used to record these results.

One may conclude from these statements that many of the abnormal manifestations in the central nervous system seen in crisis are the results of anoxia and follow the presence of excessive amounts of circulating thyroid hormone. It has long been known that the effect of administered synthetic thyroxine develops slowly (about seven hours) and lasts for a long time (five to six weeks).<sup>15</sup> The usual manifestations seen post-operatively may well not reach their maximum effect for from eight to ten days.

The profound and striking disturbances in the heat-regulating mechanism in thyrotoxicosis and thyroid crisis have evoked little experimental observation. It is known that the stimulation of the autonomic centers by artificial fevers produced with typhoid vaccines results from the stimulation of the sympatheticoadrenal system in the normal and vagotomized experimental animal.<sup>8</sup> The clinical and experimental stud-

ies carried out by Goetsch and Ritzmann<sup>9</sup> indicate that the hyperthermia is due to the action of epinephrine, whose effect is apparently enhanced in hyperthyroidism.

Jaundice has been noted and recorded on many occasions as a complication of thyrotoxicosis and particularly of thyroid crisis. Many studies have been carried out to determine whether there is any relationship between liver damage and the production of thyroid crisis, particularly that which has occurred postoperatively. No definite, consistent relationship has been noted and no prognostic evidence is forthcoming to date. Regardless of these facts the occasional patient shows profound evidence of liver damage in the course of his disease. In a few instances the clinical picture has apparently warranted a diagnosis of acute yellow atrophy. The most consistent change in the function of livers in patients with hyperthyroidism is their inability to store glycogen and to convert levulose in large amounts to dextrose. With prolonged thyroid feeding experimentally there is a profound decrease in liver, muscle, and heart glycogen. At this stage liver glycogen is easily mobilizable.

One might be tempted to ask whether epinephrine has anything to do with the liver damage seen in thyrotoxicosis; Perazzo's<sup>10</sup> work suggests that it has. He found well-advanced fatty degeneration of the liver with moderate doses of the drug.

The pathologic findings in the liver of patients dying with clinical and pathologic evidence of hyperthyroidism have been reported by many authors. There is some lack of universal agreement in the uniform location of the histopathologic changes. All are in agreement that the changes are neither pathognomonic nor of clear prognostic import. Weller<sup>11</sup> describes a patchy parenchymatous interlobular hepatitis. Beaver and Pemberton<sup>12</sup> distinguish three predominant types of lesions in exophthalmic goiter: (1) Acute degenerative lesions (fatty metamorphosis, focal and central necrosis, and changes secondary to stasis of blood); (2) simple atrophy; and (3) subacute toxic atrophy and toxic cirrhosis. The lesions described in the third classification appear among older patients, in whom the disease is of longer duration and of more than the average severity. Lord and Andrus<sup>13</sup> have more recently outlined the liver findings in their series of patients with thyrotoxicosis. They likewise describe three characteristic changes common to all patients: (1) Large droplets of fat diffusely distributed in the parenchymal cells; (2) central necrosis of the hepatic cords with marked infiltration of the necrotic areas by polymorphonuclears and erythrocytes, and (3) connective tissue proliferation in the portal areas with an infiltration of lymphocytes. McIver and Winter<sup>14</sup> have studied the deleterious effects of anoxia on the livers of experimental animals made hyperthyroid by the injection of crystalline thyroxin. Their animals were then subjected to periods of reduced oxygen concentration. The histopathologic picture of these animals shows extensive necrosis of the

liver cells about the central areas with some inflammatory cell infiltration in the portal areas. The earliest changes consisted of fatty metamorphosis and engorgement of the blood vessels in the central areas.

The liver changes just described can be produced by anoxia of an anoxic type in experimental animals in apparent hyperthyroid states; the correlation may be more than fortuitous. At present it would seem to us that the hepatic changes appearing in patients with hyperthyroidism and in thyroid crisis may well be explained on a basis of chronic anoxia in an organ already showing an increased oxygen consumption and glycogen depletion. There is at this time no substantial proof that the thyroid hormone in either exophthalmic or adenomatous goiter contains a direct cytotoxic element.

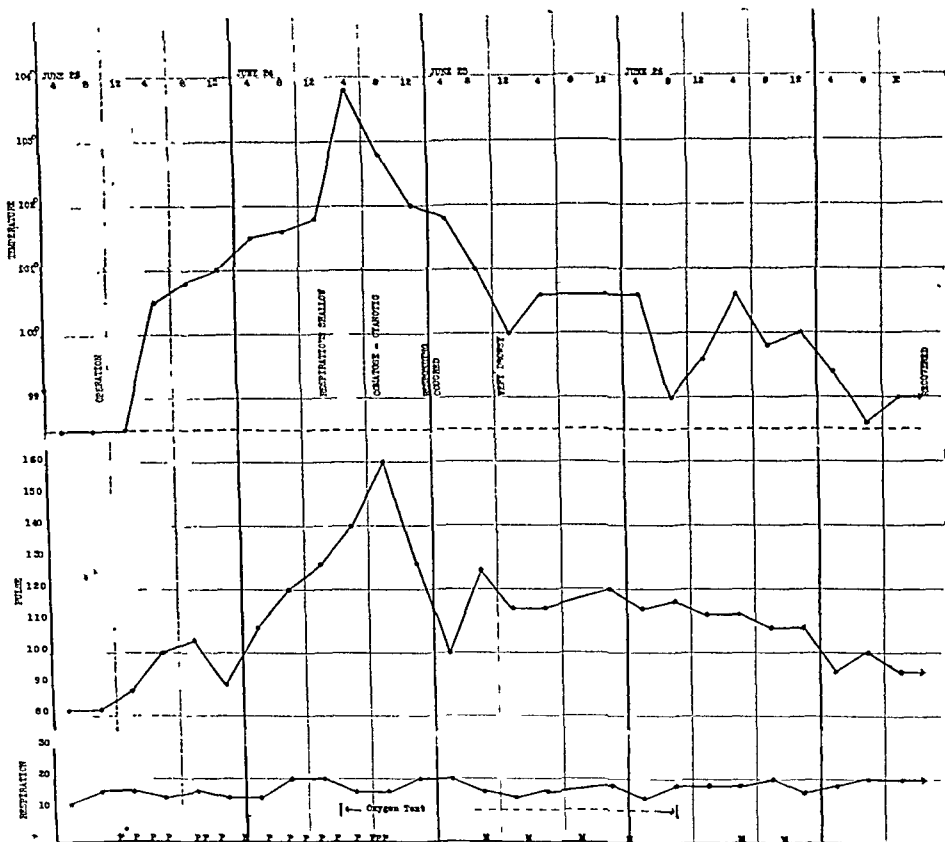
On the assumption that the opinions and facts as stated here are correct, an attempt has been made to correlate these with the findings on patients upon whom a diagnosis of thyroid crisis has been made. A small series of consecutive patients, seen over a period extending between the years 1934 to 1943 on the medical and surgical services of the University of Michigan Hospital, has been reviewed. Well over one-half of these patients died in "thyroid crisis." The greater portion of them were between the ages of 40 to 70 years. A toxic adenomatous goiter was seen in a ratio of 2:1 over the Graves' constitution thyroid. Close inspection of the records of these patients and the clinical findings present during the stage of crisis along with the available necropsy findings in those patients who died revealed that in every instance one or more factors were present to which the immediate cause of the profound symptoms and of death could be well attributed. A list of these factors includes diabetes mellitus with coma, pulmonary edema and congestion, atelectasis, hepatitis and cirrhosis, wound infection, oversedation, cardiac failure, pneumonia, septicemia, and overdigitalization. Bayley<sup>15</sup> and Ransom and Bayley<sup>16</sup> have made an analytic study of the pre- and postoperative fatalities due to thyroid crisis. Both authors emphasize certain factors in the prevention of crisis with the hope of avoiding them in the future.

The precipitating factors in preoperative crisis as summarized by them are as follows:

1. Delay in admitting toxic patients to the hospital
2. Surgical proceedings not directed at control of hyperthyroidism
3. Infections of a wide variety
4. Various minor diagnoses and therapeutic procedures
5. Inadequate sedation

We are in agreement with these conclusions. Infections, minor diagnostic and therapeutic procedures, and injudicious surgical procedures not directed at the control of an existing hyperthyroidism may undoubtedly enhance the oxygen needs of critical tissues as well as

precipitate a profound stimulation of the sympatheticoadrenal system. The role which these factors play in hyperthyroidism has been discussed. Bayley<sup>15</sup> in his study was greatly impressed by that group of patients in whom insomnia appeared to play a critical role in the production of crisis. His statement that "the value of sleep could not have been appreciated sufficiently in some of these older cases" is well taken. However, we are not in complete accord with his suggested choice of medication in the control of insomnia.



\*P. Pantopon, gr.  $\frac{1}{8}$ .

M. Morphine sulfate, gr.  $\frac{1}{4}$ .

Fig. 1.—Oversedation in the postoperative period after thyroidectomy.

The most striking and outstanding cases in our series were those in which oversedation of the patient played a predominant part in the production of the signs and symptoms. In two patients a proved drug sensitivity was present. In each of the patients there was a prompt, rising crescendo of all of the symptoms of crisis as large, frequent doses of sedatives and hypnotics were given. With increasing symptoms the frequency of drug administration, and often the amount, was stepped up, followed by a further increase in symptoms—a vicious cycle. Prompt improvement seemed apparent with diminution or cessation of these drugs (Fig. 1).

# GOITER IN CHILDREN

JOHN DEJ. PEMBERTON, M.D., AND B. MARDEN BLACK, M.D.

ROCHESTER, MINN.

(From the Division of Surgery, The Mayo Clinic)

GOITER in children differs sufficiently from goiter in adults to warrant some special study, particularly since goiter in children is unusual and experience in its management is limited. From reports in the literature<sup>1, 2, 3</sup> it would seem that there is disagreement as to whether the treatment of hyperthyroidism of children should be medical or surgical. Surgeons do not agree as to the amount of thyroid tissue that should be left behind at the time of thyroidectomy and the frequency with which carcinoma is encountered in nodular goiters of children is not fully appreciated.

With these and other differences in mind, a review of the cases of goiter in which the patients were children 14 years of age or less, encountered at the Mayo Clinic from 1908 through 1943, was undertaken and the results form the basis for this report. With the exception of adenomatous goiter with hyperthyroidism, which has not been encountered in children at the clinic, all of the major diseases of the thyroid gland which affect adults have been seen in children. Because of the number of cases involved, the report will be largely concerned with exophthalmic goiter, adenomatous goiter without hyperthyroidism, and carcinoma of the thyroid gland. The series includes 189 cases of exophthalmic goiter, 70 cases of adenomatous goiter, 18 cases of carcinoma of the thyroid gland, and 3 cases of thyroiditis.\*

## EXOPTHALMIC GOITER

Although exophthalmic goiter is the disease of the thyroid gland that is of commonest occurrence among children, patients 14 years of age or less with exophthalmic goiter constitute a small proportion of all patients suffering from this disease. Thus, at the clinic, from 1908 to 1943, inclusive, exophthalmic goiter was encountered in only 189 children. Furthermore, although the disease may have its onset even in infancy, it is distinctly rare before the age of 9 or 10 years and more than 80 per cent of children with exophthalmic goiter seen at the clinic were between 10 and 14 years of age. In children, as in adults, more females than males have the disease. The ratio of females to males in the group was 5.9:1.

The clinical picture of exophthalmic goiter in children is essentially the same as that seen in adults, with the exception that late results of the untreated disease are seen far less frequently than in adults. For

\*Prior to 1917, the ages of patients with goiter who were not operated on were not indexed. Because of this, children with nodular goiters seen at the clinic from 1908 to 1917, who were not operated on, could not be included in the study.

Received for publication, July 10, 1944.

the most part, the patients were seen at the clinic after the symptoms had persisted for less than one year, but the duration of symptoms in many cases was much longer. Helmholz<sup>1</sup> reported that nervousness was the most frequent complaint, followed by goiter, tachycardia, and exophthalmos in this order. Tachycardia was present in all cases, goiter in all but 2, nervousness in all but 2, and exophthalmos in 25 of the 30 cases in his series. He concluded that in children nervousness associated with goiter was very suggestive of the diagnosis of exophthalmic goiter. The findings in relation to symptoms in Dinsmore's<sup>5</sup> series of 57 cases were similar to those reported by Helmholz. Nervousness or goiter was the first symptom noted by the patient or his parents in 70 per cent of Dinsmore's cases and tachycardia was found in all. Less reliance can be placed on the basal metabolic rates of children than of adults; first, because of apprehension on the part of the children and, second, because the standards for children would seem to be less dependable than those for adults. Of considerable aid in the diagnosis of exophthalmic goiter in children, as in adults, is the characteristic response to administration of iodine.

Evaluation of the intensity of the disease in children is less exact than in adults and, as a rule, children suffering from exophthalmic goiter have a more severe disease than would be expected clinically. Experience has amply demonstrated that reactions to surgical measures, both at the time of operation and postoperatively, are likely to be surprisingly marked and, because of this, there is general agreement that thyroidectomy should be carried out in stages more frequently in children than in adults. However, judging from the more recent cases in the present series, it would seem that, with adequate preoperative preparation with iodine, the thyroidectomy usually can be done in one stage. Thus, the thyroidectomy was done at one sitting in 16 of the last 18 patients in whom treatment has been carried out at the clinic, and in two stages, approximately three months apart, in the remaining 2. Children should be given iodine in preparation for thyroidectomy for a materially longer period than is necessary for adults. Generally, although adults may be adequately prepared for operation by receiving iodine for approximately ten days, children will require a period of at least three weeks on iodine before operation.

*Choice and Details of Treatment.*—Although we believe that exophthalmic goiter in children is essentially the same disease as exophthalmic goiter in adults and that treatment in children, as in adults, should be subtotal thyroidectomy, it would seem that medical management by means of iodine and rest may be rarely employed, particularly in children with a mild form of the disease. Of 171 children with exophthalmic goiter seen at the clinic from 1908 to 1940, inclusive, Kennedy<sup>6</sup> was able to secure reports on the late results of treatment of 163, and of these 171, 25 had not been operated on at the clinic for various reasons. Seven of the 25 patients were subsequently

operated on elsewhere and 4 patients had died, not necessarily of hyperthyroidism. Of the 14 remaining patients, Kennedy considered the results of medical treatment to be good in 10, fair in 3, and poor in 1. Since the time of Kennedy's report, 18 children with exophthalmic goiter have been seen at the clinic and in every case thyroidectomy has been performed.

In spite of the obvious technical difficulties of thyroidectomy in very young children, and in spite of the increased tendency of children to react severely following surgical operation, the hospital mortality rate in the present series compares favorably with that following operations on adults. In all, 164 children with exophthalmic goiter were operated on at the Mayo Clinic from 1908 to 1943, inclusive, with 8 deaths, giving an over-all mortality rate of 4.9 per cent. Among 55 children operated on prior to 1922, there were 5 deaths in the hospital, which would suggest that, prior to the days of iodine preparation of patients for surgical operation, the risk to children was far greater than that to adults. However, with adequate preoperative preparation with iodine, the hospital mortality rate after thyroidectomy in children compares favorably with that of adults. Since 1921, then, 109 children have been operated on at the clinic for exophthalmic goiter with 3 deaths, or a hospital mortality rate of 2.8 per cent.

There is disagreement in published reports as to the amount of thyroid tissue that should be saved in carrying out subtotal thyroidectomy in children. Cattell,<sup>7</sup> Dinsmore,<sup>5</sup> Abbott,<sup>8</sup> and others<sup>9, 10</sup> expressed the belief that proportionately more thyroid tissue should be preserved in children than in adults and they emphasized the frequency and seriousness of myxedema following thyroidectomy in children. Welti,<sup>11</sup> and Nixon,<sup>12</sup> who quoted Means, conversely stressed the frequency of persistent hyperthyroidism and the high recurrence rate following thyroidectomy in children; they favored thyroidectomy at least as radical as that carried out in adults. In our opinion, the same relative amount of thyroid tissue should be preserved in children as in adults; and, in the present series, the thyroidectomies in children were for the most part neither more nor less radical than those done in adult patients. Following such thyroidectomies both recurrence and myxedema are not uncommon, but we do not believe the results of thyroidectomy would be bettered if greater or smaller remnants of thyroid were preserved.

*Late Results.*—It is evident, from the diversity of opinion as to the amount of thyroid tissue that should be preserved at operation for exophthalmic goiter in children, that the results in relation to myxedema and recurrence are not entirely satisfactory. However, in general, the late results in children are good and the great majority of children with exophthalmic goiter remain well following thyroidectomy. Kennedy<sup>6</sup> recently has reported the results following thyroidectomy in children with exophthalmic goiter, 14 years of age or less, seen at the clinic from 1908 to 1940, inclusive. Of the 130 patients who recovered from

operation and concerning whom reports were received, there were 4 late deaths from hyperthyroidism; in 12 cases recurrences had developed, for which 17 operations had been performed, and in 19 cases low basal metabolic rates or frank myxedema had developed. Eighteen other children with exophthalmic goiter have been operated on at the clinic since Kennedy's report, and in 1 patient of this group recurrent exophthalmic goiter has developed but so far has been successfully controlled with iodine; in 6 patients frank myxedema has developed. Follow-up in this group of 18 patients has not been continued for longer than four years.

The results following operations performed since the introduction of medication with iodine have been materially better than those of the time before iodine was used. In the group of 46 patients operated on prior to 1922, and concerning whom follow-up data are available, there were 6 recurrences, 3 late deaths from hyperthyroidism and 2 with myxedema or low basal metabolic rates. Of the 102 patients subjected to operation since 1921, and concerning whom follow-up data are available, 7 have had recurrences, 1 has died of hyperthyroidism, and 23 have developed myxedema or low basal metabolic rates. Four of the patients who had recurrences were operated on between 1922 and 1924, the fifth patient was treated in 1926, the sixth in 1930, and the last in 1939. The recurrence in this case was well controlled by means of iodine in 1943. We do not regard the development of a low basal metabolic rate or of myxedema following operation as serious as the necessity for a second operation because of recurrent exophthalmic goiter. We believe that because of the frequency of myxedema in children following operations on the thyroid gland, and because of the seriousness of unrecognized myxedema in children, they should be examined very carefully two or three months after thyroidectomy, and at subsequent intervals, so that myxedema can be adequately treated with desiccated thyroid before the child has suffered in any way.

#### ADENOMATOUS GOITER

Adenomatous goiter in children is more unusual than exophthalmic goiter in the same age group. From 1917 through 1943 only 52 cases of adenomatous goiter in which the patients were 14 years of age or less were seen at the clinic, and in none of these cases was the basal metabolic rate significantly elevated. As both Helmholz<sup>4</sup> and Kennedy<sup>13</sup> have pointed out previously, adenomatous goiter with hyperthyroidism has not been encountered in children at the clinic so that, in our experience, hyperthyroidism in children is synonymous with exophthalmic goiter. The adenomas varied in size and number, and the same pathologic variation as in adults was found in the appearance of the adenomatous tissue. The patients with adenomatous goiter ranged from newborn infants to children 14 years of age with the greatest number of patients falling in the older age groups. Nodular enlargement of the thyroid, presumably



adenomatous goiter, has been observed at the clinic in two newborn infants. As with other varieties of goiter, females were affected more frequently than males, the ratio in this group of patients being 2.7:1. Thirty-eight patients were treated by administration of iodine, of desiccated thyroid, or both, given either together or in alternate courses. Kennedy<sup>13</sup> concluded from his study of the same series of cases that the results of treatment were variable in that in some patients the goiter became smaller while in others the size remained unchanged. Enlargement of an adenoma during treatment was not observed. In those cases in which definite adenomatous enlargement persisted it was felt that subsequent surgical removal probably would become necessary.

Surgical treatment, either enucleation of the adenoma, lobectomy, or subtotal thyroidectomy was carried out in 14 patients. There were no deaths in the series. In 2 patients the basal metabolic rate postoperatively was so low that desiccated thyroid was administered, although sufficient time was not allowed to elapse in either case for the possible development of the clinical signs of myxedema.

Apart from the obvious indications for surgical treatment which have to do with the size of the goiter and its mechanical effects on surrounding structures, the possibility of malignancy is often the most important indication for exploration of a nodular goiter in an infant or child. From 1908 through 1943, of the patients 14 years of age or less, 53 with nodular goiter were operated on at the clinic.\* Of these, 32 were found to have adenomas, in 3 the nodularity was due to thyroiditis, and the remaining patients, 18 in all, had carcinomas of the thyroid gland. Stated differently, 1 of 3 nodular goiters in patients in this age group that have been explored surgically have proved to be carcinomas. It should be pointed out that in many of these cases a correct preoperative diagnosis was made, but in many other cases, as in adults, the presence or absence of malignancy was determined with certainty only at the time of operation.

#### CARCINOMA

Eighteen patients 14 years of age or less, with carcinoma of the thyroid gland, were seen at the Mayo Clinic from 1908 through 1943. Kennedy<sup>13</sup> reported that only 6 cases of carcinoma of the thyroid gland had been reported in the American literature during the twenty years prior to 1935 and he estimated that approximately 1 per cent of carcinomas of the thyroid gland occurred in children. One of us (Pemberton<sup>14</sup>) found that of a series of 774 proved cases of carcinoma of the thyroid gland, 17 of the patients were less than 20 years of age, and 4 patients were less than 10 years of age. In each of the 18 cases in the present series the diagnosis was confirmed histologically from study either of the resected specimen or of tissue removed for biopsy. In 2 cases, the specimen for biopsy was removed elsewhere but the tissue was examined here at the time that the patient was examined clinically. Carcinoma

\*See footnote page 756.

of the thyroid gland occurs about twice as often in females as in males, while in this series in children 15 patients were females and 3 were males. The age at which symptoms were first noted varied from 12 years to that of a newborn infant. The interval between the onset of symptoms and treatment varied from 4 months to 10 years, and in 12 of the 18 cases two years or more had elapsed between the appearance of the first symptoms and treatment.

Enlargement of the thyroid gland or of cervical lymph nodes was in every case the first sign of carcinoma of the thyroid. In 5 cases the enlarged cervical nodes were far more obvious than enlargement of the thyroid, which in some cases was so little evident that it was not noted in the clinical record. When a mass was present in the thyroid gland it usually was described as hard and irregular, and involved only a portion of the thyroid. In more advanced cases, as in adults, fixation to surrounding structures had occurred and symptoms of hoarseness and dyspnea were occasionally present. In only 1 case were extensive systemic effects present when the patient was first seen. Progressive enlargement of the tumor in the thyroid was noted in several cases but sudden enlargement of a pre-existing mass in the thyroid was noted rarely.

The tissue diagnosis was papillary adenocarcinoma, grade 1 in 12 cases; adenocarcinoma, grade 2 in 2 cases; adenocarcinoma, grade 4 in 1 case; papillary adenocarcinoma, grade 2 in 1 case; and adenocarcinoma, grade 1 in 2 cases. The malignant tissue was noted to be in a fetal adenoma in 1 case of papillary adenocarcinoma and in 1 case of adenocarcinoma, grade 1. Metastasis had developed at the time when the patient was first seen in 11 cases and cervical lymph nodes were involved in all of these cases. In addition, 2 patients had pulmonary metastatic growths at the first visit and in 2 other patients, later, pulmonary metastasis developed. The patient with the adenocarcinoma, grade 4 had metastatic involvement of the calvarium and spinal column when first seen at the clinic.

In 10 cases the lesion was considered operable in that it was possible to resect the involved tissue, but in the remaining 8, the disease was judged inoperable and biopsy only was done. In 2 of these cases the biopsy was carried out elsewhere. In 16 patients irradiation therapy was carried out here and in 1 case such therapy was carried out elsewhere, while the remaining patient died soon after surgical operation and before further treatment could be instituted. The results of treatment depended largely on the extent of the malignancy, but as with carcinomas of low grade of malignancy affecting the thyroid gland in adults, the time of survival after even palliative operations, combined with adequate irradiation therapy, was often surprisingly long.

#### THYROIDITIS

There were 3 cases of thyroiditis in the series and in each case the question of possible malignancy was raised clinically. One patient, a

boy 12 years of age, had a diffusely enlarged but somewhat nodular thyroid. His basal metabolic rate was -19 per cent but there were no signs of myxedema. He was treated with iodine and desiccated thyroid. In this case the diagnosis was not proved. The other 2 patients were treated surgically. The thyroid of a boy of 13 years was firm, nodular, and slightly tender. The basal metabolic rate was -6 per cent. Subtotal thyroidectomy was carried out and, following the operation, the basal metabolic rate was -14 per cent. There were no signs of myxedema. The last patient, a girl of 13 years, had a firm, nodular thyroid with a basal metabolic rate of -13 per cent. Subtotal thyroidectomy was carried out.

#### ADOLESCENT GOITER

It is difficult to make any statement concerning the incidence of adolescent goiter in children, because different observers do not agree as to what constitutes an abnormal enlargement of the thyroid gland. It would seem that diffuse, symmetrical enlargement of the thyroid gland is rarely seen at the clinic in children 14 years of age or less and that the condition is very unusual prior to the onset of puberty. In most patients seen at the clinic, when a frank goiter was encountered in this age group, the condition was treated with iodine, desiccated thyroid, or both. In some, after such treatment had been instituted, the diffuse enlargement of the thyroid gland was reduced so that adenomas became palpable. Such cases have been considered under the heading of adenomatous goiters. In the very early years covered by the study, several patients with large, adolescent goiters were operated on, but such patients have not been encountered at the clinic for many years.

#### SUMMARY

From 1908 through 1943, 189 children 14 years of age or less with exophthalmic goiter were seen at the Mayo Clinic. In most cases thyroidectomy was carried out at the clinic, but 14 patients were treated medically with results that were considered good in 10, fair, in 3, and poor in 1. Thyroidectomy was performed in 164 patients, 8 dying while in the hospital. Fifty-five patients were operated on during the period before medication with iodine was instituted, with 5 deaths. One hundred nine children have been operated on after having been prepared for operation with iodine, with 3 deaths, for a hospital mortality rate of 2.8 per cent. Since the use of iodine began, the late results after thyroidectomy have been satisfactory. In the group of 102 patients who survived operation done since the use of iodine was instituted, and on whom follow-up data are available, 1 patient died from the results of hyperthyroidism. 7 patients have had recurrent exophthalmic goiter, and 23 patients developed low basal metabolic rates or myxedema.

Fifty-two children 14 years of age or less with adenomatous goiter were seen at the clinic from 1917 through 1943. In no case was the

basal metabolic rate elevated and adenomatous goiter with hyperthyroidism has never been encountered in children at the clinic. Fourteen patients were operated on and the remainder were treated medically. The adenomas seemed to differ in no way from those found in the goiters of adults.

From 1908 through 1943, 53 children with nodular goiters were operated on here. In 32 cases the nodularity was caused by adenomas, in 3 cases by thyroiditis, and in 18 cases by malignancy. In 5 cases of carcinoma, enlarged cervical lymph nodes overshadowed the enlargement of the thyroid but, in the other 13 cases, the nodularity was largely confined to the thyroid gland. Thus, 1 in 3 nodular goiters in children, for which operation has been performed at the clinic, have been malignant.

In 17 of the 18 children with carcinoma of the thyroid gland, the tissue diagnosis was adenocarcinoma of malignancy either grade 1 or grade 2. Thirteen of the adenocarcinomas were of the papillary type, and 2 were noted to have developed in fetal adenomas. In 1 case the adenocarcinoma was of malignancy grade 4. The lesion was judged operable in 10 cases, inoperable in 8. In every case in which metastasis had developed, 11 in all, the cervical lymph nodes were involved; in 4 cases pulmonary metastasis developed and in 1 case metastatic tissue was found in the calvarium and spinal column. Whether the lesion was resected or not, irradiation therapy was carried out except in 1 case, in which death occurred following biopsy.

#### REFERENCES

1. Bram, Israel: Exophthalmic Goiter in Children; Comments Based Upon 128 Cases in Patients of 12 and Under, *Arch. Pediat.* 54: 419-424, 1937.
2. Kerley, C. G.: Hyperthyroidism in Children, *Arch. Pediat.* 58: 92-96, 1941.
3. Pierce, A. W.: Hyperthyroidism in Childhood, *Texas State J. Med.* 37: 740-743, 1942.
4. Helmholtz, H. F.: Exophthalmic Goiter in Childhood, *J. A. M. A.* 87: 157-162, 1926.
5. Dinsmore, R. S.: Hyperthyroidism in Children; a Review of Fifty-seven Cases, *J. A. M. A.* 99: 636-638, 1932.
6. Kennedy, R. L. J.: Surgical and Medical Treatment of Exophthalmic Goiter in Children; Late Results, *Am. J. Dis. Child.* 60: 677-684, 1940.
7. Cattell, R. B.: Diseases of the Thyroid in Children, *Tr. Am. A. Study Goiter*, pp. 239-246, 1933.
8. Abbott, A. C.: Some Observations on Hyperthyroidism in Children With a Report on Seven Cases, *Internat. Clin.* 4: 98-108, 1932.
9. Lehman, J. A.: Hyperthyroidism in Children, *West. J. Surg.* 44: 528-534, 1936.
10. Rankin, F. W., and Priestley, J. T.: Exophthalmic Goiter in Children; a Review of Ninety-one Cases, *Tr. Am. A. Study Goiter*, pp. 120-127, 1932.
11. Welti, H.: *Maladie de Basedow chez l'enfant*, *Tr. Third Internat. Goiter Conference and Tr. Am. A. Study Goiter*, pp. 101-107, 1938.
12. Nixon, N.: Treatment of Graves' Disease in Children, *J. Pediat.* 18: 71-83, 1941.
13. Kennedy, R. L. J.: Nodular Goiter Among Infants and Children, *Tr. Am. A. Study Goiter*, pp. 322-326, 1940.
14. Pemberton, J. deJ.: Malignant Lesions of the Thyroid Gland; a Review of 774 Cases, *Surg., Gynec. & Obst.* 69: 417-430, 1939.

## GOITER IN THE SOUTHERN STATES

HOWARD MAHORNER, M.D., NEW ORLEANS, LA.

GOITER is not common in the southern states. Although southern surgeons have contributed in a meager proportion to the literature on goiter, in recent years more and more papers have appeared from this section showing at last a growing realization that though most of the South is not an endemic goiter region, its peoples have goiter not infrequently and in some sections in surprisingly high incidence. In the coastal states of the South, goiters in Negroes offer unique problems not observed in like prominence in series from endemic goiter regions of the nation. The distribution of goiter in the South is irregular. In general the incidence is low, but in sporadic sections not truly goiter belts, more goiter is found than is average for the South. Goiter is probably encountered most commonly in the mountainous regions, particularly in the more thickly settled parts of the Appalachian range. Brenizer and McKnight<sup>1</sup> reported 7,500 goiter operations performed by them in Charlotte, N. C., over a period of twenty-eight years. S. L. Ledbetter,<sup>2</sup> of Birmingham, and Earle Drennen,<sup>3</sup> of Birmingham, each have performed over 1,000 operations for goiter. Scruggs<sup>4</sup> reported that in 123 hospitals affiliated with the Duke Foundation, or 85 per cent of the hospitals of North Carolina, there were 893 thyroid operations performed in 1938. Hayne<sup>5</sup> found goiters in 3.8 per cent of 17,600 people examined throughout South Carolina. Davison and Poer<sup>6</sup> reported 542 cases of goiter from the records of the Henry Grady Hospital and from their own practice in Atlanta covering a period of ten years. They stated that during 1935 there were only 350 operations for goiter in the entire state of Georgia. In 1939, Mahorner and Barrow<sup>7</sup> reported 248 patients with goiter among 52,863 patients admitted in one year to Charity Hospital in New Orleans (1 to 213). Only 105 patients of this group were operated upon for goiter. Lehman and Shearburn<sup>8</sup> found 401 surgical goiter patients among 87,661 admitted to the University of Virginia Hospital over a period of twelve years. Less than 0.1 per cent of men from the southern states examined for the draft in World War I showed goiter,<sup>9</sup> whereas, in the same draft examinations from 1.5 to 3 per cent of the men from the Northwest and Great Lakes Regions were found to have goiter. All of these reports from different sections of the South attest to the relative infrequency of goiter and to the few surgeons with large experience in this field. In spite of the fact that goiters are not as common as they are in endemic goiter regions, thyroid diseases of all variety and all degrees of severity are encountered in the South.

Goiters occur more frequently in the southern part of Louisiana than in the central and northern areas of the state. Olesen<sup>10</sup> in his report on the distribution of endemic goiter in the United States revealed some astounding figures. In parishes (the counties of other states) in the southern part of Louisiana the incidence of goiter in children was stated to be from 35 to 55 per cent in boys and from 38 to 70 per cent in girls. This estimate is far from correct. Even though it is well appreciated that more goiter is found in the flat southeastern part of Louisiana, it is obvious to those of us who see patients from the parishes around New Orleans, that goiters are not as common as Olesen's figures indicate.

I computed<sup>11</sup> the number of goiter patients admitted in 1938 to three charity hospitals in Louisiana, at Lafayette, Shreveport, and New Orleans. They were divided according to the parish from which they came. The number of patients admitted from southern parishes was greater than the number admitted from other sections; and this not only was true of total number of patients admitted, it was also true expressed as the incidence of goiter per 10,000 inhabitants of each parish. Thus from Orleans parish there were 1.9 per 10,000, from Lafourche, Terrebonne and St. Bernard parishes adjacent to Orleans there were 2.15, 3.0, and 5.5, respectively, per 10,000 inhabitants. In northern parishes the incidence was 0.5 to 1.5 per 10,000. This is admittedly a very gross and inexact method of estimating the distribution of goiter, mainly because it is incomplete, does not include all hospitals, and does include only indigent patients of the state in one year. However, these findings corroborate the impression long since held by the profession of this community that goiter is not uncommon among peoples inhabiting the banks of certain bayous. These rivers, often very deep, were originally estuaries of the Mississippi River. The surrounding lands are flat and low and frequently marshy and were formed by alluvial deposits of the Mississippi River. The diet of the people inhabiting this area consists presumably of much sea foods, and the iodine content of their vegetables is relatively high. The people themselves along these bayous recognize that nodular goiters are common. The explanation as to why the people in this low flat area should have more goiters than those in the rest of Louisiana is not available. All the soil of this area was brought down the river possibly from the upper Mississippi and the Ohio Rivers, which drain goiter belts. A positive goiterogenic factor thus may have been transported, but another engaging thought is the possibility of a negative factor being responsible for the goiters. The water supply for many of these families is rain water from cisterns.

Many reports from the South show a high mortality for thyroid surgery. This in general is true and has usually been explained by less experience with the management of the disease. However, there is danger of being overapologetic for the higher mortality, for a few

southern surgeons record mortality rates for thyroidectomy which are unsurpassed in excellence. Drennen<sup>12</sup> in Birmingham reported 300 thyroidectomies with 1 death. In his entire series of over 1,100 operations for goiter, he has had but 5 deaths,<sup>3</sup> a mortality of less than one-half of 1 per cent. Ledbetter<sup>2</sup> in the same city, since 1929, has performed over 1,400 operations with no deaths. Scruggs<sup>4</sup> of Charlotte, N. C., reported 256 operations for goiter with 1 death. While these three series are not large, they attest to excellent surgical judgment and technique.



Fig. 1.—A Negro woman, aged 58 years, with severe exophthalmic goiter before, and one year after, operation. The operation was done in stages under unfavorable hospital facilities with good result. Goiters of this type in the Negro race deserve management with extra caution.

Many southern authors have called attention to the higher mortality in Negro patients. Goiters occur as frequently or more frequently in the Negro race than in the white race.<sup>11</sup> Lehman and Shearburn reported 401 thyroidectomies in a twelve-year period at the University of Virginia Hospital. The mortality was almost entirely in the Negro race. The mortality figures for white patients was 0.84 per cent and for Negroes 9.4 per cent. They could not explain the higher mortality in Negroes after an analysis of data, and they believe that the disease in the Negro may be surgically a separate problem. Bigger<sup>13</sup> also admitted a higher mortality in the Negro and thinks it due in part to malnutrition and vitamin deficiency in that race. Maes, Boyce and McFetrich (1936)<sup>14</sup> reported the total mortality for thyroid operations as 5.7 per cent in the Charity Hospital series. The deaths (medical) from goiter in patients not operated upon for the same period exceeded the postoperative deaths. In Negro men with toxic goiter the mortality for thyroidectomy was 25 per cent. Maes believes that thyroid disease is a severer and graver condition in the Negro man than the same disease in white individuals. In a later publication Boyce<sup>15</sup> reported 817 surgical thyroid cases from the same institution (Charity Hospital) and again called attention to the high mortality in the Negro. The total mortality was 5.3 per cent. The mortality following thy-

roidectomy for toxic goiter was higher in the Negro race (12.58 per cent) than in the white race (6.93 per cent). He says the reason for this disproportion existing baffles explanation. Herrmann<sup>16</sup> reported 40 Negroes among 729 patients with goiter admitted to the surgical service of the Lakeside Hospital, Cleveland. He could find no difference in the severity of the disease or in the response to treatment between Negro and native white people. While it is true that various series show a higher mortality for thyroid surgery in the Negro, a higher mortality for hyperthyroidism in the Negro without surgery has not been reported. Should this be true it would be a significant finding, particularly in such series as those from Charity Hospital where the medical deaths exceeded those following surgery.

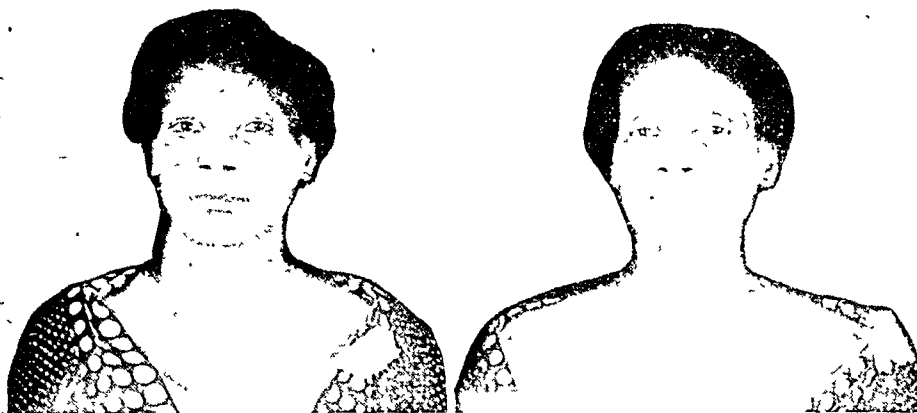


Fig. 2.—A Negro woman, aged 38 years, before and after operation for a huge toxic nodular goiter (weight approximately 600 Gm.). The substernal portion was also very large. On admission she had cardiac decompensation. She came from lower Mississippi where goiter is not common. This is an example of the extent to which sporadic goiter may develop in a nonendemic area. She became perfectly well following thyroidectomy.

I have had a higher mortality for thyroidectomy in Negroes, however, my impressions of the causes for this are not in accord with some of the previously expressed reasons. As far as I can observe the disease is similar in course and average severity in the Negro. The response to preoperative preparation is less prompt and less decided in the Negro, but that in my experience is due to less favorable physical surroundings such as noise, crowding, too many visitors, and ward hospitalization in very hot, poorly ventilated space equipped only with basic essentials. Facilities entirely devoid of luxuries may be of no significance in the favorable outcome for most patients, but for the severely sick patient a luxury may become an essential and be a deciding factor in recovery.

During 1942, 1943, and 1944 (through October) on my services at Touro Infirmary, the Baptist Hospital, and the Eye, Ear, Nose, and Throat Hospital, I performed 110 operations for goiter on 101 patients. Seven of the patients had multiple stage operations (two patients had



three operations). This is a very small group of patients, but in this section of the country it may not be considered small and is representative of goiters as they are encountered here. Indeed, practically all variety of goiters were encountered.

Sixty-one patients represented the white race whereas forty were Negroes. There were only 7 men to 94 women, a ratio of 1 to 13.

Fifty-five of the patients had toxic goiters and forty-six nontoxic nodular goiters. The pathologist reported Hashimoto's disease in two instances. Four patients had substernal goiters. One patient with a toxic goiter was a child (girl) aged 13 years.

Of the patients who had multiple stage operations, five were white and two were Negroes. Two patients died following operation. Both were colored women with toxic diffuse (exophthalmic) goiters. Both deaths occurred postoperatively within two days, presumably of thyroid crises. These two deaths were both preventable and could have been avoided by stage operations. Other patients in this group were more severely toxic and were graver risks, yet they were carried successfully through their operations. Each of the two Negro patients who died had far less favorable physical surroundings for their illness, yet I must admit that the judgment as to the time and extent of operation was exerted just as if they were surrounded with the excessive luxuries afforded by many of the other patients in this group. The deficiencies in the facilities of the Negro patients should be countered with more cautiousness, which means more prolonged and more careful preparation and more frequent stage operations, not fewer than in white patients.

In my experience it has not been possible to produce conditions for Negro patients entirely favorable to surgery for toxic goiter. The economic part is largely the answer, for even though they may be very sick, a bed in a ward together with patients with various other conditions, entailing the commotion and excitement of visitors and many people in the room at one time, is frequently the best condition available for the important period of preoperative preparation and postoperative care. Even if the economy factor could be obviated there are others which often prevent optimum conditions and facilities being arranged for some of these very sick patients. Moreover, in the Negro there is an additional chance on the part of the surgeon for misjudgment of the proper time and extent of operation in toxic goiter. Ordinarily the Negro tolerates surgery well. His constitution and endurance are usually good. This should not confuse one but it probably has confused many. Moreover, no matter how sincerely the surgeon wishes to ignore them for better evidence upon which to base the soundest judgment, economic conditions in this day of crowded hospitals, even if the patient is provided for by eleemosynary funds, sometimes influence judgment to hasten the operation date. Other factors resulting from the relative infrequency of the condition in the South, such as technical errors, contribute to the higher mortalities, but it appears

that the main lesson to be learned from these repeated reports of higher mortality in the Negro is a lesson in judgment, namely, the necessity of being more wary, more cautious, when dealing with goiter in that race than when dealing with a condition of similar severity in a white patient. It is already well established that elderly individuals and children do not tolerate operation as well as those in middle decades. Goiter in the Negro should be added to these groups to emphasize the increased cautiousness which might be absolutely essential to obtaining a satisfactorily low mortality. This is not, as it might seem, a contradiction; the risk for the Negro race is still equivalent to the risk for the white race, but extra precautions must be taken to offset the physical handicaps in their hospitalization and other elements in judgment as to the proper time and the proper extent of operation.

#### SUMMARY

Goiter is not common in the southern states. It occurs most frequently in the mountainous areas. A few southern surgeons, however, report mortality rates for thyroid surgery which are unsurpassed in excellence.

The mortality for thyroid surgery in the Negro is in general higher than that for white patients. Poorer facilities for hospitalization and impetuous judgment may be the dominating factor in this higher mortality rate. A group of seventy patients from my private services is reported.

#### REFERENCES

1. Brenizer, Addison G., and McKnight, Roy B.: True Adenomas of the Thyroid Gland and Their Relation to Cancer, *Tr. Am. A. Study Goiter*, p. 176, 1940.
2. Ledbetter, S. L.: Personal communication.
3. Drennen, Earle: Personal communication.
4. Scruggs, Wm. M.: Thyroidectomy Under Avertin Anesthesia, *Tr. Am. A. Study Goiter*, p. 50, 1940.
5. Hayne, J. A.: Endemic Goiter and Its Relation to Iodine Content of Food, *Am. J. Pub. Health* 19: 1111, 1929.
6. Davison, T. C., and Poer, D. H.: Goiter in Georgia. A Statistical Study of Five Hundred and Forty-two Cases, *Tr. Am. A. Study Goiter*, p. 184, 1936.
7. Mahorner, Howard, and Barrow, Woolfolk: Goiter in the Deep South, *Tr. Am. A. Study Goiter*, 1939.
8. Lehman, Edwin P., and Shearburne, E. W.: Thyrotoxicosis Including a Study of the Duration of Preoperative Treatment, *Tr. South. S. A.* 51: 72, 1938.
9. McClendon, F. A., and Williams, A.: Simple Goiter as a Result of Iodine Deficiency, *J. A. M. A.* 80: 600, 1923.
10. Olesen, Robert: Distribution of Endemic Goiter in the U. S. as Shown by Thyroid Surveys, *U. S. Public Health Reports* 44 (Part I): 1463, 1929.
11. Mahorner, Howard: Surgical Management of Goiter, *New Orleans M. & S. J.* 94: 129, 1941.
12. Drennen, Earle: An Analysis of 300 Consecutive Thyroidectomies, *Ann. Surg.* 105: 717, 1937.
13. Bigger, I. A.: Discussion of Lehman and Shearburn's Paper, *Tr. South S. A.* 51: 72, 1938.
14. Maes, Urban, Boyce, F. A., and McFetrich, Eliz. M.: Further Observations on Thyroid Disease in a Non endemic Area, *Tr. South. S. A.* 49: 60, 1936.
15. Boyce, Frederick F.: Factors in the Mortality of Thyroid Disease in a Non-endemic Area, With a Note on the Value of the Quick Test of Liver Function in the Estimation of Hepatic Damage, *South. Surgeon* 9: 96, 1940.
16. Herrmann, Lewis G.: Thyro-toxicosis in the Negro, *Surg., Gynec. & Obst.* 55: 221, 1932.

## THYROIDITIS

NATHAN A. WOMACK, M.D., ST. LOUIS, MO.

*(From the Department of Surgery, Washington University School of Medicine  
and the Barnes Hospital)*

THYROIDITIS, when defined as the reaction of the thyroid gland to injury, is commonplace. Degenerative changes with subsequent fibrosis are demonstrable in most nodular goiters and probably play an important part in the formation of the nodularity. The thyroid is a labile organ and responds functionally in the maintenance of oxygen consumption at a certain level. Frequently in physiologic and pathologic states of stress, such an increase in function is required in the maintenance of homeostasis. With this increase in function there is often a demonstrable morphologic alteration in individual cells and even groups of acini.<sup>1</sup> As a result of the interplay of several factors residual damage may be seen as evidenced by change in acinous size and shape, extravasation of colloid into the surrounding stroma, vascular damage, fibrosis, and even calcification. These changes are characteristically seen in nodular goiters and, in the broad sense, represent inflammation. In this consideration of the subject of inflammation of the thyroid gland, however, thyroiditis will be discussed in which the inflammatory process per se is apparently the cause of symptoms. These are usually encountered clinically under three main types: (1) acute suppurative thyroiditis; (2) acute nonsuppurative thyroiditis; (3) chronic degenerative thyroiditis.

### ACUTE SUPPURATIVE THYROIDITIS

Acute suppurations are of bacterial origin, and strangely enough, are extremely uncommon, when compared to the frequency of metastatic abscesses in many other organs of the body. The thyroid gland seems to possess a definite resistance to local infection. In unpublished work, Cole and I<sup>2</sup> found that when pure cultures of streptococci and staphylococci were injected directly into the superior thyroid artery of dogs, abscess formation rarely followed. This was the experience of Roger and Garnier<sup>3</sup> in a more elaborate series of experiments. And yet these infections are obviously embolic when they do occur, either being associated with a generalized septicemia or following shortly after an acute infection in the pharynx or upper respiratory tract. The most common organisms encountered are the staphylococcus and streptococcus groups, although almost any type may be present. We have encountered the colon bacillus on two occasions and the typhoid bacillus once.

---

Received for publication, July 10, 1944.

The onset of the disease is often abrupt, being associated with chills occasionally, but always fever and local evidence of inflammation. Pain is the outstanding symptom. Because of the close relationship with the ribbon muscles of the neck, and the resulting spasm of these structures, the patient prefers to keep the neck in flexion, often in a sitting posture. Swallowing is painful and even hoarseness may be encountered. While the abscesses at first may be multiple, they are generally limited to one lobe or the isthmus. As a result, along with the diffuse swelling present in the neck, there may be present eccentric swelling. Where the isthmus of the thyroid is involved the depression above the sternal notch is often filled. The thyroid gland can usually be palpated but the outlines are masked by edema, and examination is difficult because of tenderness.

The systemic reaction to the infection is usually marked, perhaps due to the organ involved as well as its relation to the respiratory tract. Rupture into the trachea may occur but this is rare. If untreated, extension into the deep spaces of the neck is the most common sequela, and this is of grave consequence.

Since the advent of chemotherapy, acute suppuration of the thyroid gland is becoming less frequent. However, when an abscess does occur, surgical drainage is indicated along with suitable chemotherapeutic measures. Adequate oxygen intake is of the greatest importance and the use of the oxygen tent is advisable. The surgical incision must give adequate drainage, and this will entail a good exposure of the part. At the same time, care must be taken not to break through the inflammatory barriers of the neck more than is necessary, and in particular, pathways to the mediastinum must be protected.

Cases are on record in which so much thyroid tissue was destroyed by the infection that myxedema resulted. This, however, is extremely rare, and a good result should be obtained although this, to a large extent, will depend on the severity of the generalized infection, of which the suppuration in the thyroid is a part.

#### ACUTE NONSUPPURATIVE THYROIDITIS

Nonsuppurative acute thyroiditis is seen more frequently than the suppurative type, and yet very little is known about it. It is recognized by its clinical manifestations, but surgical interference is seldom indicated, and adequate bacteriologic and morphologic observations are, therefore, not available. In view of the fact that about one-half of the patients will give a history of recent upper respiratory tract infection and that occasionally the process goes on to suppuration, it is probable that the instigating factor in the inflammation is bacterial.

The symptomatology resembles the suppurative type in character, but not in extent. The onset is not so abrupt and the general manifestations are mild. Fever is slight or absent. The thyroid is enlarged and tender, but swelling and tenderness throughout the soft tissues

are generally considered at the present time as representing different pathologic pictures, and presenting different clinical syndromes.<sup>12, 15-23</sup> A critical opinion, however, on the evidence in support of two distinct pathologic entities is certainly equivocal.

When these lesions are considered as separate entities, the dominant characteristic of Riedel's disease is fibrosis. In about one-third of the reported cases, this has been limited to one lobe or a part of one lobe. Extraglandular fibrosis, however, is present in later stages as has been seen in earlier reported cases. The involved gland is hard and white and usually not appreciably enlarged, although when the surrounding muscles and large vessels are involved, the outlines of the gland are not too distinct.

In the earlier stages, this fibrous tissue may be very cellular and there is a considerable infiltration of cells of the lymphocytic series often with follicle formation. Supposedly, one of the most characteristic features is the thyroid parenchyma. It is often enmeshed in the fibrosing process, but the thyroid acini are said to be normal. This has not been our experience. Careful study of the thyroid acini has shown definite evidence of cellular injury in most instances and this injury has resulted in hyperplasia, metaplasia, and what apparently is the retention of secretory products in the cytoplasm resembling the so-called Hürthle cell. Cell death is the end result. This may be gradual, the acinus becoming smaller and smaller, or many cells may degenerate at once leaving unabsorbed colloid in the stroma. At such time, giant cell reaction is present, and the giant cell often takes on bizarre appearances because of the resemblance of the colloid to its cytoplasm. It is quite possible that the rapidity of this process may determine the degree of the inflammatory reaction.

The most conspicuous clinical features are related to the fibrosis. If this is mild, a slightly enlarged, very hard gland may be the presenting symptom. As fibrosis progresses, and more thyroid tissue is destroyed, evidence of hypofunction of the gland may be present. Often in the very early stages, however, a slight hyperfunction may exist for a short while. Invasion of adjacent structures by the fibroblasts brings on symptoms of obstruction. Compression of the jugular veins with resulting edema, and pressure on the esophagus causing dysphagia are usually earlier than severe tracheal obstruction. When the lesion is limited to one lobe, respiratory difficulty may appear, due to tracheal displacement. Recurrent laryngeal nerve involvement is extremely rare.

The most difficult lesion to exclude is cancer, and while often one may make the presumptive diagnosis of Riedel's struma, certainty is usually not established until operation, and even then microscopic examination of the tissue may be necessary. The massive fibrosing type is extremely rare, apparently may occur in the relatively young although this has not been our experience, and males are frequently affected.

The treatment is entirely related to relief or prevention of obstruction. When only one lobe or a part of a lobe is involved, resection of

this lobe and the isthmus is generally feasible. Where the entire gland and contiguous structures are involved, subtotal resection is usually fraught with considerable danger and removal of the isthmus in order to free the trachea may be all that can safely be accomplished. There have been several favorable reports from the use of x-ray therapy but this has been with the more cellular type of lesion.

The classical picture of struma lymphomatosa as it is generally considered presents several differences. The entire gland is usually involved when the patient first presents herself, although not necessarily so. The gland is lobulated, very thick, and the surface smooth. The only extraglandular attachments encountered are tracheal, and these never extensive. This gross picture is easily explained when the gland is studied microscopically. The yellow trabeculated, meaty appearance of the cut surface is due to lymphoid overgrowth. Lymphoid follicles are prominent, but the lymphocytes themselves as well as the structure of the follicle differ in type in no way from those encountered less extensively in exophthalmic goiter, status thymolympathicus, or even Riedel's struma. The chief difference appears to be a quantitative one. In the earlier stages the gland is friable, but later it is more resilient as fibrosis increases. One of the impressive microscopic lesions is in the thyroid parenchyma. The Hürthle cell type of degeneration described in Riedel's struma is much more marked and almost universal. Giant cell reaction about the colloid is also more pronounced. Fibrosis is present in varying amounts and it is perhaps the relationship between the relative amounts of lymphoid follicle tissue and fibrosis that has led to most of the confusion in classifying various types of thyroiditis.

The clinical picture associated with the type of lesion found in struma lymphomatosa has been for the most part vague and associated with the mild compressive symptoms that one would anticipate. Neither hyperthyroidism nor hypothyroidism are, as a rule, outstanding in most early cases. After thyroidectomy, hypothyroidism is frequently observed. It is stated that these patients are practically always 50 years old or more. It is also generally stated that the lesion does not occur in men. One may readily question the statistical accuracy of such statements as being based on entirely too small a number of clinical observations.

Surgical extirpation of most of the gland has been the treatment of choice. Most operations have been performed with a mistaken diagnosis, and one may well doubt the value of surgical extirpation where obstruction is not important. Often hypothyroidism is the end result and this certainly is not prevented by surgery. Following thyroidectomy hoarseness may be present for many months. Where a diagnosis could be established, radiation has been reported to be of value.<sup>24</sup> It would seem that here, as in Riedel's struma, the chief damage produced by this lesion is that of obstruction, and here the indication for surgical extirpation must lie.

As has been stated there exists a considerable controversy as to the relationship between Riedel's struma and Hashimoto's type of struma lymphomatosa. In isolated, well-defined types, there seems to be a definite difference in the clinical picture. Clinical syndromes, however, owe their existence to underlying pathologic disturbance, and the answer to the question will be much easier to obtain by an analysis of the pathologic picture, rather than a study of statistical reports. It seems apparent from a consideration of the microscopic appearance of these two lesions that they present a quantitative, rather than a qualitative, difference, and the symptoms that ensue are related to the predominance of a particular type of inflammatory reaction. In Riedel's goiter, it is fibrosis; in Hashimoto's type it is lymphoid overgrowth. Often both have been noted in almost equal amounts, and this has led to discussions as to classification that have not been too illuminating.

It has been assumed by some that the fibrosis is an end stage of the lymphadenoid type, but evidence to support this very logical assumption is not too apparent. Observations have been recorded on cases in which microscopic studies have been made at intervals of two years<sup>16</sup> and thirteen years<sup>25</sup> with no great amount of change in the microscopic picture. It is therefore much more likely that they represent parallel manifestations of the same underlying injury.

Infections of various types have been thought at times to play a part in the production of these changes. Cultures of the glands whenever done have, for the most part, been sterile, and such changes were not encountered when bacteria were injected directly in the superior thyroid arteries of dogs and rabbits by Cole and me.<sup>2</sup> This does not mean, however, that infection may not play an indirect role. Upper respiratory tract infections have been frequently noted in the cases reported, and while this association may be fortuitous, it still must be borne in mind. It has been suggested recently<sup>26</sup> that Riedel's thyroiditis may be the result of a perithyroiditis with vascular occlusion. That it may be the result of iodine effect<sup>14</sup> has been considered, and McCarrison<sup>27</sup> has reproduced a lesion in rats showing a definite microscopic resemblance to struma lymphomatosa, by certain dietary deficiencies. McKnight<sup>28</sup> has suggested that the inflammation is secondary to an obscure biochemical irritant probably produced by the patient. None of these etiological concepts, however, fits the complete clinical picture.

As has been stated, the interstitial lymphoid nodules with their germinal centers differ in no way except in amount from those seen in other thyroid lesions and in particularly exophthalmic goiter. All of these lesions seem to represent functional aberration on the part of the entire gland or some of its cells, and wherever lymphoid hyperplasia is seen in the thyroid there usually is evidence of an unusual absorption of secretory products or of cellular degeneration and breakdown. It is not a constant finding with all functional atrophy, however, as it is not commonly seen following anterior lobe hypophysectomy in the experimental

animal or in Simmonds' disease. Again, as may be noted in Fig. 1, neither lymphoid hyperplasia nor fibrosis is seen in atrophy where the human gland has been exposed to large amounts of radiation. The loose acellular collagen here surrounds minute acini, and probably represents the result of the action of the irradiation on the vascular apparatus.

However, there are times in which an inflammatory reaction to colloid is most marked, and whether the colloid undergoes a chemical change as has been suggested by Mallory,<sup>29</sup> the reaction seems to be related definitely to its fatty acid content as has been demonstrated by Ferguson.<sup>30</sup> He showed that in disintegrating follicles as a result of the hydrolysis of the lipids in the colloid and epithelium an extensive inflammatory reaction may occur with giant cell formation, lymphoid hyperplasia, and fibroplasia. Goetsch, however,<sup>31</sup> believes the giant cells are

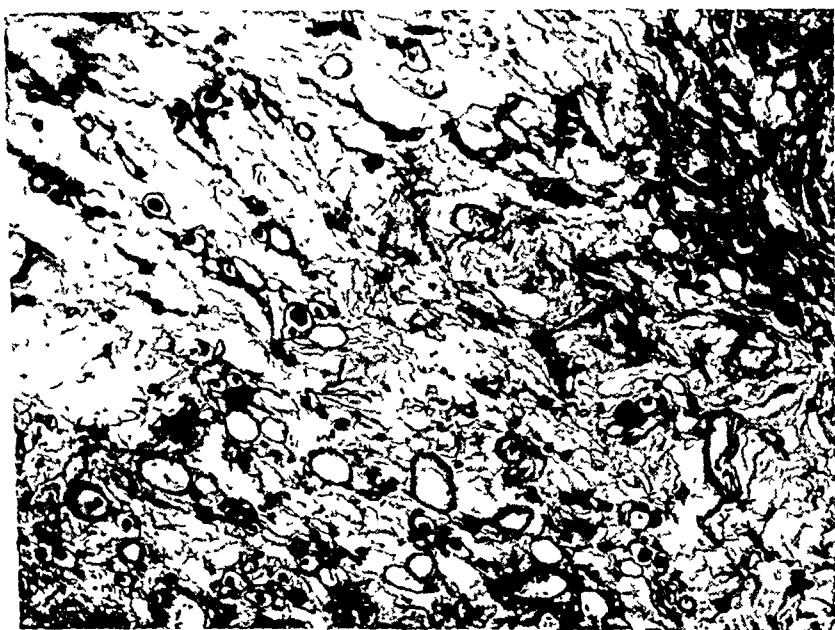


Fig. 1—Effect of extensive x-ray therapy on thyroid showing changes secondary to avascularity. Note loose collagen fibrils and absence of dense fibrosis as well as lymphoid reaction.

composed of a syncytium of degenerating thyroid cells and are not phagocytic, and he interprets them as evidence of the degenerative process that takes place in Riedel's disease associated with the inflammatory reaction. Fig. 2 illustrates this type of parenchymatous change as seen associated with marked reaction to the colloid and the degenerating thyroid parenchyma.

Thus, degeneration of the thyroid cells and the colloid can be demonstrated as a fairly constant finding in chronic thyroiditis. The cause of this degeneration is not so easily found. Since this finding is so universally associated with function, endocrine interrelationships must necessarily be studied. Apparently the anterior lobe of the hypophy-



sis, the islets of Langerhans, the parathyroids, and the adrenal medulla play no part. The sex hormones have been inadequately studied to warrant any definite conclusions. The effect of the adrenal cortex is much more suggestive. Lymphoid hyperplasia in adrenal cortical insufficiency is an old observation, being most dramatically seen in the thymic enlargement that occurs in status thymolympathicus. Pituitary adrenotrophic effect on lymphoid tissue mass has been recently demonstrated<sup>38</sup> as has the action of adrenal cortical hormone in experimental leukemia suggested hormone effect on the lymphoid systems.<sup>39</sup> Similar changes in the thyroid as we have noted in both the Riedel and the Hashimoto types of gland have been noted by many observers as being associated with adrenal cortical hypoplasia.<sup>32-36</sup> The adrenal lesion is more commonly that of a cytotoxic type of atrophy rather than that

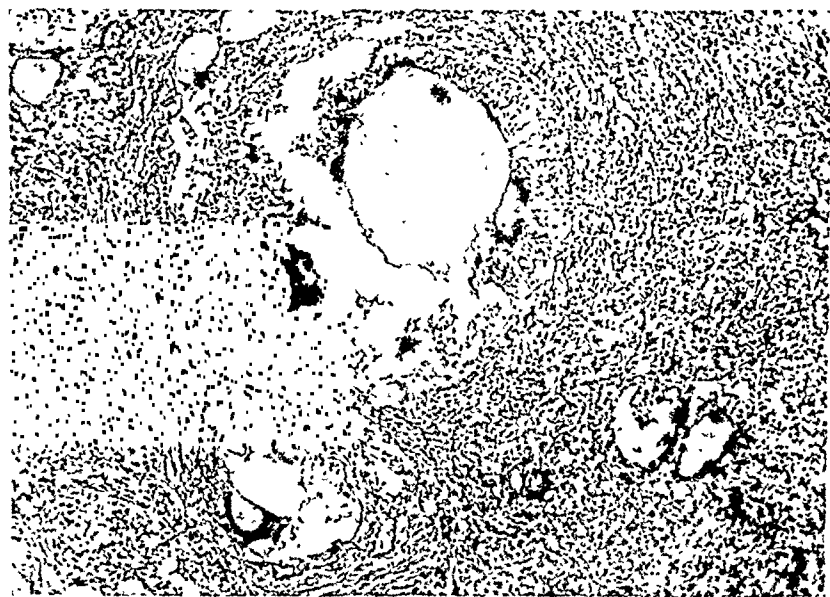


Fig. 2.—Inflammatory reaction to colloid. There apparently has been rapid epithelial degeneration. There are foam cells as well as giant cells around the colloid suggesting a reaction to lipids.

seen in tuberculous destruction. Figs. 3 and 4 illustrate the resemblance between the thyroid seen in such adrenal insufficiency and Riedel's struma, while Figs. 5 and 6 compare the Hashimoto type of thyroiditis with another area from the thyroid of the same patient with cortical insufficiency. When studied in great detail but little difference is noted. However, while it is not unusual to find such changes in the thyroid in this type of adrenal cortical insufficiency, these changes have also been noted in the thyroid in which the adrenal cortex was apparently normal. Jaffé has reported four such instances.<sup>37</sup> In each of his cases extensive lymphocytic infiltration was noted, and in two of them extensive fibrosis was present. In three of these cases the thyroid lesions



Fig. 3.—Area from Riedel's struma illustrating fibrosis and round-cell infiltration.

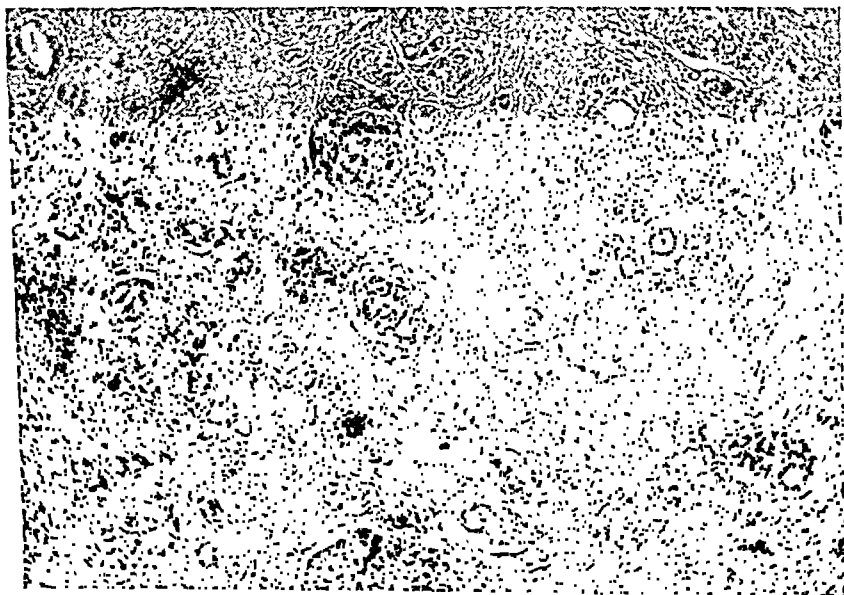


Fig. 4.—Area from thyroid gland of patient dying from cytotoxic type of adrenal cortical insufficiency showing similar changes to those encountered in Riedel's struma.



Fig. 5.—Massive lymphoid overgrowth as seen in Hashimoto type of thyroid.

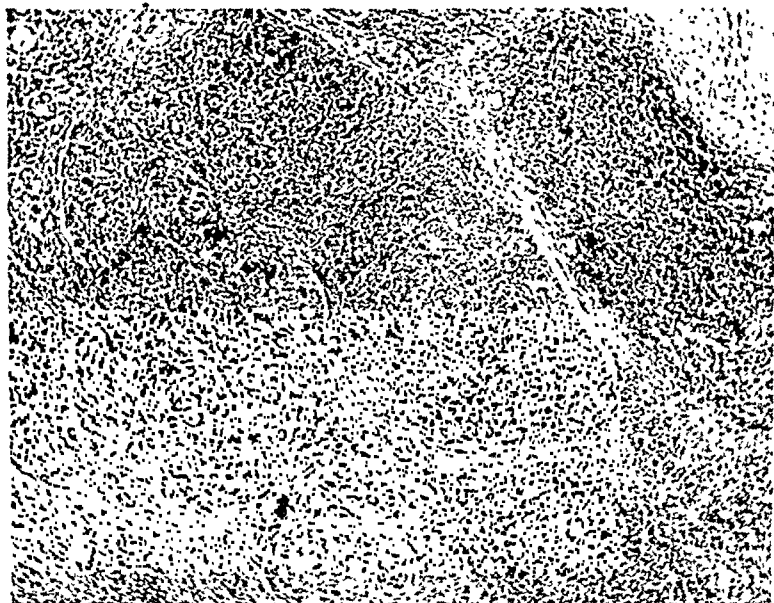


Fig. 6.—Lymphoid overgrowth and parenchymatous atrophy in thyroid of same patient as shown in Fig. 4. Compare with Hashimoto type of lesion seen in Fig. 5.

were incidental autopsy findings, with no symptoms referable to the thyroid, while the fourth showed evidence of myxedema. The changes noted in the adrenal were, for the most part, slight and consisted chiefly in alteration in lipid dispersion. He thus felt that the lymphocytic infiltration and fibrosis so often seen in the thyroid in atrophy of the adrenal cortex "is not secondary to the destruction of the cortex but is a separate, although coordinate, process." Furthermore, Scaresello and Goodale<sup>25</sup> have described the autopsy findings in a patient with struma lymphomatosa in which no gross lesion was noted in the adrenal glands. Detailed microscopic observations were not given in their protocol. The failure to note extensive morphologic changes in the adrenal, however, does not exclude functional alterations.

In summary, therefore, some aspects of Riedel's thyroiditis and Hashimoto's struma lymphomatosa must still remain controversial. Several features, however, are becoming definite. They both represent inflammatory processes, and are nonbacterial in origin. While clinically they may present divergent pictures as a result of the type of inflammatory change noted in the thyroid gland, pathologically this change is of the same basic type, and the diversions are quantitative rather than qualitative. The lymphoid overgrowth and the fibrosis are associated with a reaction to a peculiar type of parenchymatous degeneration which may be responsible for the inflammation, but may not be responsible entirely for the massive lymphocytic reaction. The cause of the degeneration of the thyroid cells needs to be investigated more fully. It is of great interest to note that identical changes in the thyroid are often seen in adrenal cortical insufficiency, even though at times they may also be present without demonstrable morphologic lesions in the adrenal cortex. Further studies of the endocrine relationships must be made, and in particular is there a dearth of information regarding the action of the steroid hormones of the sex glands.

#### REFERENCES

1. Womack, N. A., and Cole, W. H.: Normal and Pathologic Repair in the Thyroid Gland, *Arch. Surg.* 23: 466, 1931.
2. Cole, W. H., and Womack, N. A.: Unpublished observations, 1928.
3. Roger, H., and Garnier, M.: La Glande Thyroïde dans les Maladies infectieuses, *Compt. rend. Soc. de biol.* 50: 889, 1898.
4. Semple, R. H.: Fibroid Enlargement of the Thyroid Body With Enlarged Cervical Nodes, *Tr. Path. Soc., London* 20: 397, 1869.
5. Bowlby, H. A.: Infiltrating Fibroma (Sarcoma) of the Thyroid Gland, *Tr. Path. Soc., London* 36: 420, 1885.
6. Riedel, B. M. C. L.: Die chronische, zur Bildung eisenharter Tumoren führende Entzündung der Schilddrüse, *Verhandl. d. deutsch. Gesellsch. f. Chir.* 25: 101, 1896.
7. Riedel, B. M. C. L.: Vorstellung eines Kranken mit chronischer Strumitis, *ibid.* 26: 127, 1897.
8. Riedel, B. M. C. L.: Ueber Verlauf und Ausgang den Strumitis chronica, *München. med. Wchnschr.* 57: 1946, 1910.
9. Hashimoto, H.: Zur Kenntnis der Lymphomatösen Veränderung der Schilddrüse (Struma Lymphomatosa), *Arch. f. klin. Chir.* 97: 219, 1912.
10. Ewing, James: Neoplastic Diseases, Ed. 2, Philadelphia, 1922, W. B. Saunders Company.

11. Williamson, G. S., and Pearse, I. H.: Lymphadenoid Goiter and Its Clinical Significance, *Brit. M. J.* 1: 46, 1929.
12. Graham, A., and McCullagh, E. P.: Atrophy and Fibrosis Associated With Lymphoid Tissue in the Thyroid, *Arch. Surg.* 22: 548, 1931.
13. Eisen, D.: Relationship Between Riedel's Struma and Struma Lymphomatosa, *Canad. M. A. J.* 31: 144, 1934.
14. Boyden, A. M., Collier, F. A., and Bugher, J. C.: Riedel's Struma, *West. J. Surg.* 43: 547, 1935.
15. Lee, J. G.: Chronic Non-Specific Thyroiditis, *Arch. Surg.* 31: 982, 1935.
16. McClintock, J. C., and Wright, A. W.: Riedel's Struma and Struma Lymphomatosa (Hashimoto), *Ann. Surg.* 106: 11, 1937.
17. Lee, C. M., Jr., and McGrath, E. J.: Struma Lymphomatosa (Hashimoto), *SURGERY* 2: 238, 1937.
18. Joll, C. A.: The Pathology, Diagnosis and Treatment of Hashimoto's Disease, *Brit. J. Surg.* 27: 351, 1939.
19. Ziskind, J., and Schattlenberg, H. J.: Struma Lymphomatosa (Hashimoto), *Am. J. Surg.* 49: 378, 1940.
20. Harry, N. M.: Riedel's Disease and Lymphadenoid Goiter, *M. J. Australia* 2: 595, 1940.
21. Goodman, H. I.: Riedel's Thyroiditis, *Am. J. Surg.* 54: 472, 1941.
22. Moore, E. C., and Lloyd, O. D.: Hashimoto's Disease (Struma Lymphomatosa), *Am. J. Surg.* 57: 513, 1942.
23. McSwain, B., and Moore, S. W.: Struma Lymphomatosa (Hashimoto's Disease), *Surg., Gynec. & Obst.* 76: 562, 1943.
24. Renton, J. M., Charteris, A. A., and Heggie, J. F.: Riedel's Thyroiditis and Its Treatment by Radium, *Brit. J. Surg.* 26: 54, 1938.
25. Scarcello, N. S., and Goodale, R. H.: Struma Lymphomatosa, *New England J. Med.* 224: 60, 1941.
26. De Courey, J. L.: A New Theory Concerning the Etiology of Riedel's Struma, *SURGERY* 12: 754, 1942.
27. McCarrison, Col. R., I. M. S.: Note on the Experimental Production of Lymphadenoid Goiter in Rats, *Brit. M. J.* 1: 5, 1929.
28. McKnight, R. B.: Riedel's Thyroiditis, *South. Surgeon* 5: 375, 1936.
29. Mallory, F. B.: Principles of Pathologic Histology, Philadelphia, 1918, W. B. Saunders Company, page 658.
30. Ferguson, J. A.: Tissue Reaction to Colloid and Lipoids From the Human Thyroid Gland, *Arch. Path.* 15: 244, 1933.
31. Goetsch, E.: Origin, Evolution and Significance of Giant Cells in Riedel's Struma, *Arch. Surg.* 41: 308, 1940.
32. Dubois, M.: Ueber das Vorkommen lymphatischer Herde in der Schilddrüse bei Morbus Addisonii, *Berlin Klin. Wehnschr.* 56: 1178, 1919.
33. Schmidt, M. B.: Eine biglanduläre Erkrankung (Nebennieren und Schilddrüse) bei Morbus Addisonii, *Verhandl. d. deutsch. path. Ges.* 21: 212, 1926.
34. Heim, W.: Diabetes Mellitus und Addisonsche Krankheit (M. B. Schmidt), *Frankfurt. Ztschr. f. Path.* 54: 250, 1940.
35. Kothe, H.: Der Status thyreo-suprarenalis (M. B. Schmidt), *Endokrinologie* 22: 229, 1939.
36. Rushton, J. G., Cragg, R. W., and Stalker, L. K.: Spontaneous Hypoglycemia Due to Atrophy of the Adrenal Glands, *Arch. Int. Med.* 66: 531, 1940.
37. Jaffé, R. H.: Chronic Thyroiditis, *J. A. M. A.* 108: 105, 1937.
38. White, A., and Dougherty, T. F.: Influence of Pituitary Adrenotrophic Hormone on Lymphoid Tissue Structure in Relation to Serum Proteins, *Proc. Soc. Exper. Biol. & Med.* 56: 26, 1944.
39. Murphy, J. B., and Sturm, E.: The Effect of Adrenal Cortical and Pituitary Adrenotropic Hormones on Transplanted Leukemia in Rats, *Science* 99: 303, 1944.

## MALIGNANT GOITER

ROBERTSON WARD, M.D., SAN FRANCISCO, CALIF.

*(From the Department of Surgery, University of California Medical School)*

**M**ALIGNANCY is relatively rare in the field of thyroid surgery. However, it is important to know which types of goiter are likely to become malignant and which signs should arouse suspicion of malignant change. Cancer is almost unknown in exophthalmic goiter; indeed, so few cases have been reported that the diagnosis of exophthalmic goiter virtually eliminates the likelihood of its presence. In our series of 5,439 thyroidectomies there were 168 cases of cancer. Only one of these occurred in the exophthalmic type. It has been pointed out<sup>1, 16</sup> that although diffuse toxic goiter rarely gives rise to carcinoma, the microscopic picture in certain regenerative hyperplastic goiters is difficult to distinguish from that of malignant thyroid growths.

### RELATION OF NODULAR GOITER TO CARCINOMA

With diffuse toxic goiter eliminated from consideration, it will be seen that the problem of cancer of the thyroid gland revolves about nodular goiter. The logic of this is apparent on contemplating the following facts. It has long been recognized and taught that a large proportion of malignant goiters have their origin in malignant degeneration of primarily benign and often long-standing tumors of the thyroid gland. Moreover, cancers of the thyroid, like those elsewhere, arise from a single focus, and in their local growth are seen as tumors or nodules rather than as diffuse infiltrations of the gland. Primary carcinoma arising in a previously normal thyroid gland, however, is probably not so rare as statistics would lead us to believe. Computed figures on this point are far from accurate for two reasons. First, many patients are unaware of the presence of fairly large goiters, and become conscious of them only when malignant change increases the rate of growth. Second, many primarily malignant goiters grow slowly or remain dormant for long periods of time. However, the mere fact that a tumor has existed for many years previous to its surgical removal does not necessarily indicate that the growth was benign at its inception. A recent review of the records of patients treated for goiter at the University of California Hospital during the past five years showed sixty-eight in which the history of pre-existing goiter seemed trustworthy. Of these sixty-eight, there were thirty-two in whom the history suggested very strongly that the tumor had been malignant from the onset. A number of patients were unaware that goiter had pre-existed the neoplasm, and in some the growth itself

Received for publication, July 10, 1944.

was discovered only after the removal of metastatic nodules in distant regions had led to examination of the thyroid gland. This illustrates that data obtained from questioning patients are notably inaccurate and may lead to false premises. In this connection, I reported thirty-six malignant goiters in 1930,<sup>13</sup> concluding that 94 per cent arose from goiters which had existed for varying periods of time before our examination, and that only two of the thirty-six were definitely not adenomatous in origin. In the light of recent experience, I now believe this conclusion to be unjustified.

The role played by pre-existing goiter as a source of carcinoma may have been decidedly overemphasized. However, in making a diagnosis of malignancy or suspected malignancy, too much stress cannot be laid on the significance of the nodular type of goiter. Almost all malignant goiters are nodular.

#### AGE

In general, the age groups of patients affected by carcinoma of the thyroid are comparable to those of patients affected by carcinoma of other organs. Approximately two-thirds of these patients are seen in the three decades between 40 and 70 years of age, while less than one-fifth are afflicted before the age of 40 years. There is, however, one rather remarkable feature which should be constantly borne in mind, namely, that malignancy appears in aberrant thyroid tissue at a much earlier age. The accompanying graphs show that in a previously reported series<sup>16</sup> the majority of malignancies occurring in laterally placed thyroid tissue were seen in patients under the age of 30 years (Fig. 1).

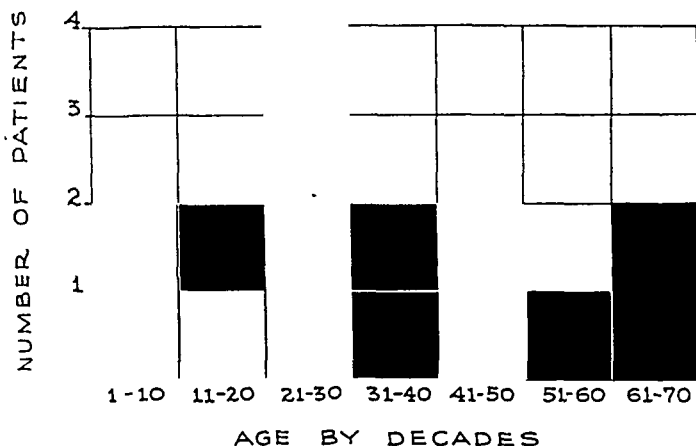
#### INCIDENCE

The frequency with which malignancy of the thyroid gland occurs has never been determined, and accuracy in such an estimate is impossible. There is little question, however, that geographical location and the incidence of nodular goiter are important factors in its production.<sup>14</sup> Wegelin<sup>17</sup> concluded that where goiter is endemic, malignant tumors of the thyroid occur in greater number. Wilson<sup>18</sup> pointed out that while autopsies in Bern, Switzerland, showed 1 death in 93 from malignant goiter, the figures from the United States revealed only 1 death in 928 from this type. The incidence of malignancy in surgically treated goiters varies from the high figures of 6.5 to almost 10 per cent reported by Kocher<sup>9</sup> and de Quervain<sup>12</sup> in Switzerland, to less than 1 per cent reported by Eberts and associates<sup>5</sup> in Canada. In the United States, the frequency is between 1.5 and 2.5 per cent. In my latest compilation of statistics, the incidence was 168 malignancies in 5,439 surgically treated goiters, or 3 per cent. Of these 5,439 cases in which pathologic specimens were available for examination, 1,900 could be eliminated as being of the diffuse type, leaving 168 malignancies in 3,539 cases, an incidence of 4.8 per cent.

## SEX

An interesting feature of sex incidence which has not received sufficient emphasis in the literature is that, while the actual number of men with malignant goiter reported in all series of cases is less than that of women, the expectancy of carcinoma in men with nodular goiter is much greater. As I pointed out in 1935 and again in 1940, although the proportion of surgical goiters in men compared to women

### AGE DISTRIBUTION OF PATIENTS WITH MALIGNANT LATERAL ABERRANT THYROIDS



### AGE DISTRIBUTION OF 95 PATIENTS WITH MALIGNANT GOITER NOT OF LATERAL ORIGIN

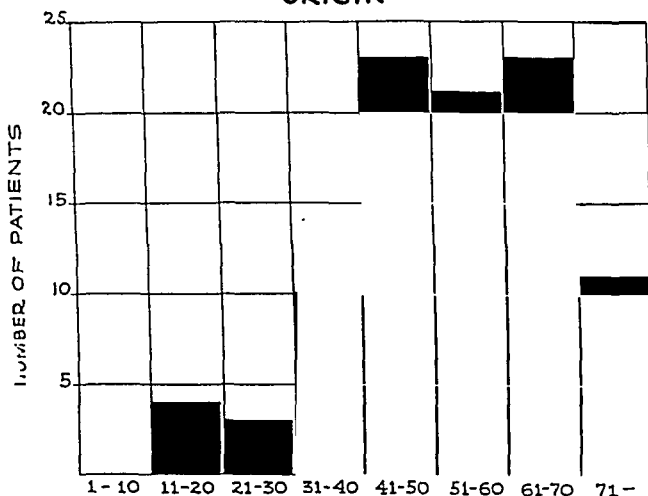


Fig. 1.—Graphs illustrating early age at which cancer of aberrant thyroid tissue is seen as contrasted with that of midline origin.



TABLE I

GOITER STATISTICS FROM UNIVERSITY OF CALIFORNIA HOSPITAL THROUGH 1943

SEX	SURGICAL GOITERS	TOXIC DIFFUSE GOITERS	NODULAR GOITERS	MALIG- NANT GOITERS	MALIGNANT TO NODULAR GOITERS	
					RATIO	PER CENT
Male and Female	5439	1900	3539	168	1:21	4.8
Male	698	335	363	41	1:90	11.0
Female	4741	1565	3176	127	1:25	4.0
Male:Female	1:6.8.	1:4.6	1:8.7	1:3		

is about 1 to 7, the ratio of malignant goiters is 1 in men to 3 or 4 in women. Thus, in this series of patients with nodular goiter, there was 1 carcinoma to each 17 men, but only 1 to each 44 women.

In the three years, 1941 to 1943 inclusive, there were 102 surgical goiters in men at the University of California Hospital. Seven of these proved to be malignant, an incidence of 1 carcinoma to each 15 patients operated upon. If the diffuse toxic goiters, of which there were 52, are eliminated, the almost unbelievable figure is obtained in men of 1 malignant out of each 7 nodular goiters coming to surgery, or 14 per cent. Table I shows the comparative rate of malignancy in men and women in the present series. The point to be kept in mind is that in men nodular goiter is many times more likely to be malignant than it is in women.

## DIAGNOSIS

A definite preoperative diagnosis of malignant goiter should seldom be made. If one waits for the textbook picture, the time for surgical cure has passed. All diagnostic signs of malignancy are based upon penetration of the capsule of the gland and involvement of surrounding tissues. The hoarseness results from infiltration of the recurrent nerves; the fixation is caused by infiltration of the trachea or ribbon muscles; and the hardness is dependent upon the outward growth of cancerous tissue to replace normal, soft thyroid gland. Of these three cardinal signs, all can be found in benign nodular goiter. Although rare, paralysis of one or the other laryngeal nerve can be caused by pressure from a benign tumor. Davis<sup>4</sup> found this to be true in 0.4 per cent of cases. Fixation comparable to that accompanying infiltration of surrounding tissues can result from retrosternal and retrotracheal

TABLE II

PATHOLOGIC CLASSIFICATION OF MALIGNANT TUMORS OF THYROID GLAND SHOWING APPROXIMATE PERCENTAGE OF TUMORS IN EACH GROUP

	PATHOLOGIC CLASSIFICATION	PER CENT
Group I (low malignancy)	Papillary carcinoma	36
Group II (moderate malignancy)	A. Malignant adenoma, Langhans	22
	B. Malignant adenoma, fetal	12
Group III (hopeless)	All others, including medullary, scirrhus, anaplastic carcinoma, sarcoma, and mixed types	28

extensions of benign adenomatous nodules. The same hard consistency as that encountered in malignant goiter will often be found in long-standing adenomatous nodules which have undergone calcareous degeneration. In this connection, however, it is not safe to assume that malignancy is absent because calcification in portions of the thyroid gland has been demonstrated roentgenologically. Carcinomatous and calcareous degeneration in the same nodule (Fig. 2) is not infrequent. Carcinoma may be suspected from the history alone in cases in which a long-standing or slowly growing tumor begins to increase rapidly in size and produce pressure symptoms. Operative treatment should be recommended on presumptive evidence of this kind, and should not be deferred until the previously mentioned cardinal symptoms have developed. As will be pointed out in the discussion of prognosis, no delay is justified in order to assure a more certain diagnosis.

#### PATHOLOGIC TYPES

There have been almost as many classifications of malignant neoplasms as there have been students of the subject. From a clinical point of view, the simplest classification which aids the surgeon to arrive at an accurate prognosis and institution of adequate therapy is the best. Most of the confusion in classifying cancer of the thyroid gland arises from a lack of uniformly accepted criteria of malignancy. Without going into detail regarding the different arrangements in use, suffice it to state that these tumors must be grouped according to their characteristics of growth as well as their microscopic architecture. Any classification is difficult because of the extreme variability presented by the lesions and the absence of a definite dividing line between benignancy and malignancy as judged by histologic studies. Criteria of malignancy based on cytologic changes alone are notoriously unreliable. The invasive qualities of a tumor have come to be recognized as the most dependable indication of the presence of malignancy, as well as of its degree. Without this invasive quality, an encapsulated tumor cannot be said to be malignant, regardless of its microscopic pattern.

A universally accepted classification would be of the greatest advantage in comparing parallel series of cases reported by different authors. Most writers have accepted Graham's<sup>6</sup> criterion of malignancy, namely, invasion of blood vessels. To this has been added as definite evidence of malignancy, invasion of the capsule of the adenoma, of its lymphatics, or of surrounding thyroid tissue and muscle. The classification used by Clute and Warren<sup>2</sup> is valuable. In their arrangement, cases are roughly divided into three grades: those of low or potential malignancy, those of moderate but not hopeless malignancy, and those of extreme or hopeless malignancy. The grouping used by me<sup>15</sup> is still simpler; it is based upon the reports of many observers that papillary tumors of the thyroid show the best prognosis. For this reason, all papillary tumors are

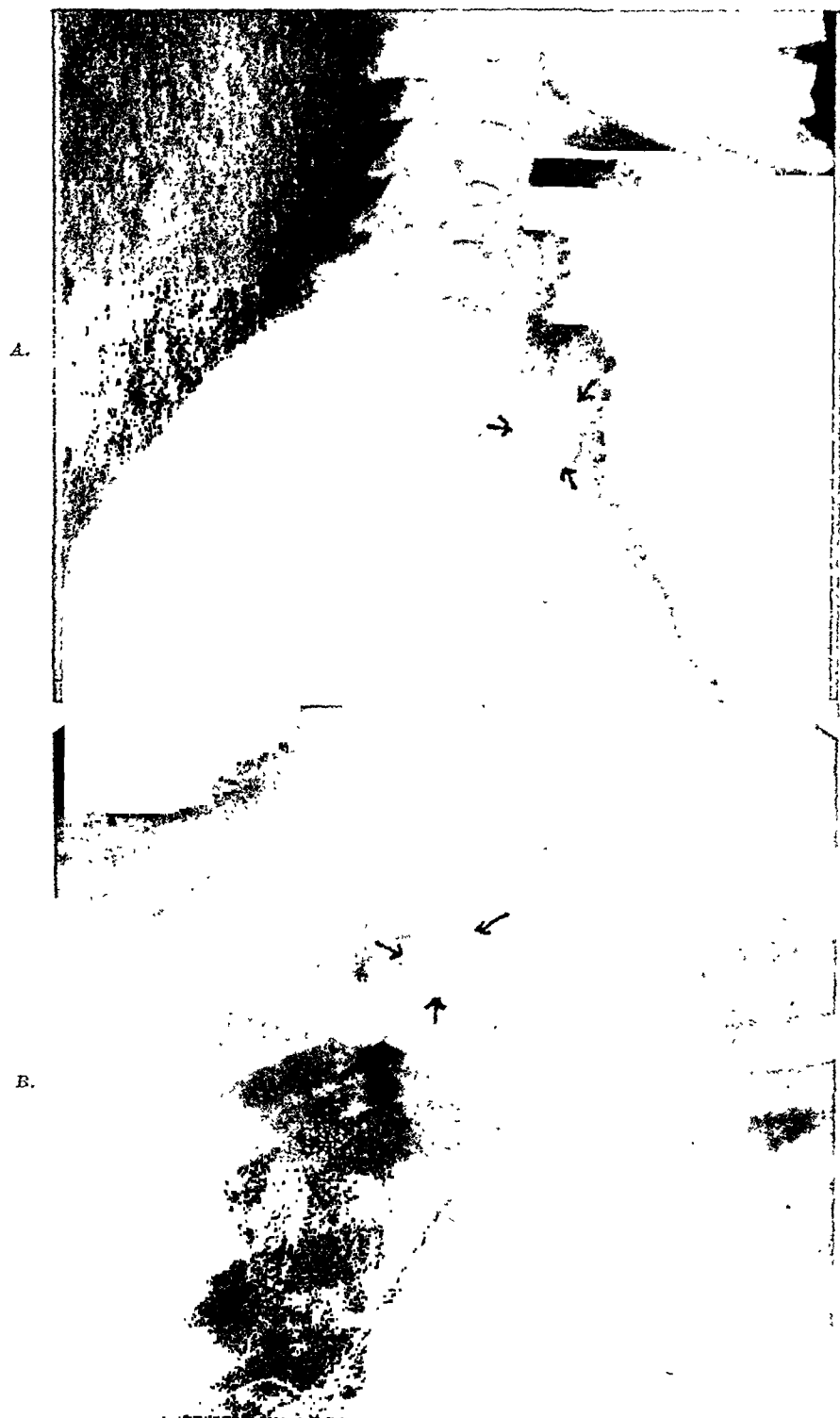


Fig. 2.—Roentgenograms A and B illustrating calcified areas in carcinoma of thyroid gland.

placed in a separate classification, irrespective of their origin in adenomas, aberrant thyroid tissue, or the gland proper. Since few carcinomas of the thyroid show a pure cellular pattern, and since the response to radiation therapy as well as the prognosis is peculiarly dependent upon the presence and amount of papilliferous tissue, this classification is based upon the presence and proportionate quantity of such tissue in the tumor. Roughly, from a prognostic and therapeutic standpoint, it is practical to arrange thyroid tumors in the following groups: Group I, papillary carcinomas; Group II, malignant adenomas; Group III, all others, including scirrhus, small cell, and large cell types, undifferentiated carcinomas, and those which display a sarcomatous tendency (Table II).

Group II is based upon gross findings, namely, an adenoma which has undergone malignant degeneration. In order to compare this series with those of Continental observers, our group has been subdivided arbitrarily into: A, Langhans' struma, those tumors showing the picture described by Langhans as proliferating adenoma (wuchernde Struma); and B, all other malignancies arising in an adenoma called "fetal" for lack of a more descriptive term. Fig. 3 illustrates variations of the papillary design, Fig. 4 typical Langhans pattern, and Fig. 5 a number of the more anaplastic tumors included in Group III. In the following section it will be seen how this classification is of value in reaching a more accurate prognosis.

#### PROGNOSIS

There are three principal factors upon which prognosis is based. These are the time of diagnosis, the pathologic pattern, and the presence of metastasis. A recent survey of the material available to me has shown, as would be expected, that the easier the diagnosis the worse the prognosis. By dividing patients into three groups, as shown in Table III, it will be seen that of those bearing a preoperative diagnosis of malignancy or suspected malignancy, only 20 per cent survive for five years or longer. Of those in whom the malignancy is discovered first at the time of operation, 40 per cent survive five years. Eighty per cent in whom malignancy is first demonstrated upon section of the specimen removed live for five years, only one in five being likely to suffer recurrence. This is understandable when it is recalled that diagnosis before operation is based on involvement of extrathyroid tissue, diagnosis at

TABLE III

## PROGNOSIS

	AFTER 5 YEARS	
	PER CENT DEAD	PER CENT LIVING
Group I (carcinoma diagnosed or suspected)	80	20
Group II (carcinoma diagnosed at operation)	60	40
Group III (diagnosed first on pathologic examination)	20	80



C.

B.

A.

Fig. 3.—Three examples of papillary tumors. A ( $\times 120$ ) is from patient (Case 71) in whom papillary tissue was mixed with anaplastic tumor which caused death in three months. B ( $\times 120$ ) is from patient (Case 20) who survived eleven years, responded well to irradiation, and died of pleural infiltration from anaplastic metaplasia of original tumor. C ( $\times 80$ ) is from patient (Case 9) who should have responded well to modern radiation therapy, but was operated on twice for recurrences and died eight months after original operation.



Fig. 4.—Three representative views of malignant adenoma, Langhans. A ( $\times 80$ ) is from a Swiss patient and is typical of original Langhans' description. B ( $\times 36$ ) is from the 9-year-old boy whose chest films are shown in Fig. 7. C ( $\times 450$ ) is from lateral deposits in neck of 16-year-old girl, who has now reached 30 years of age without signs of recurrence.



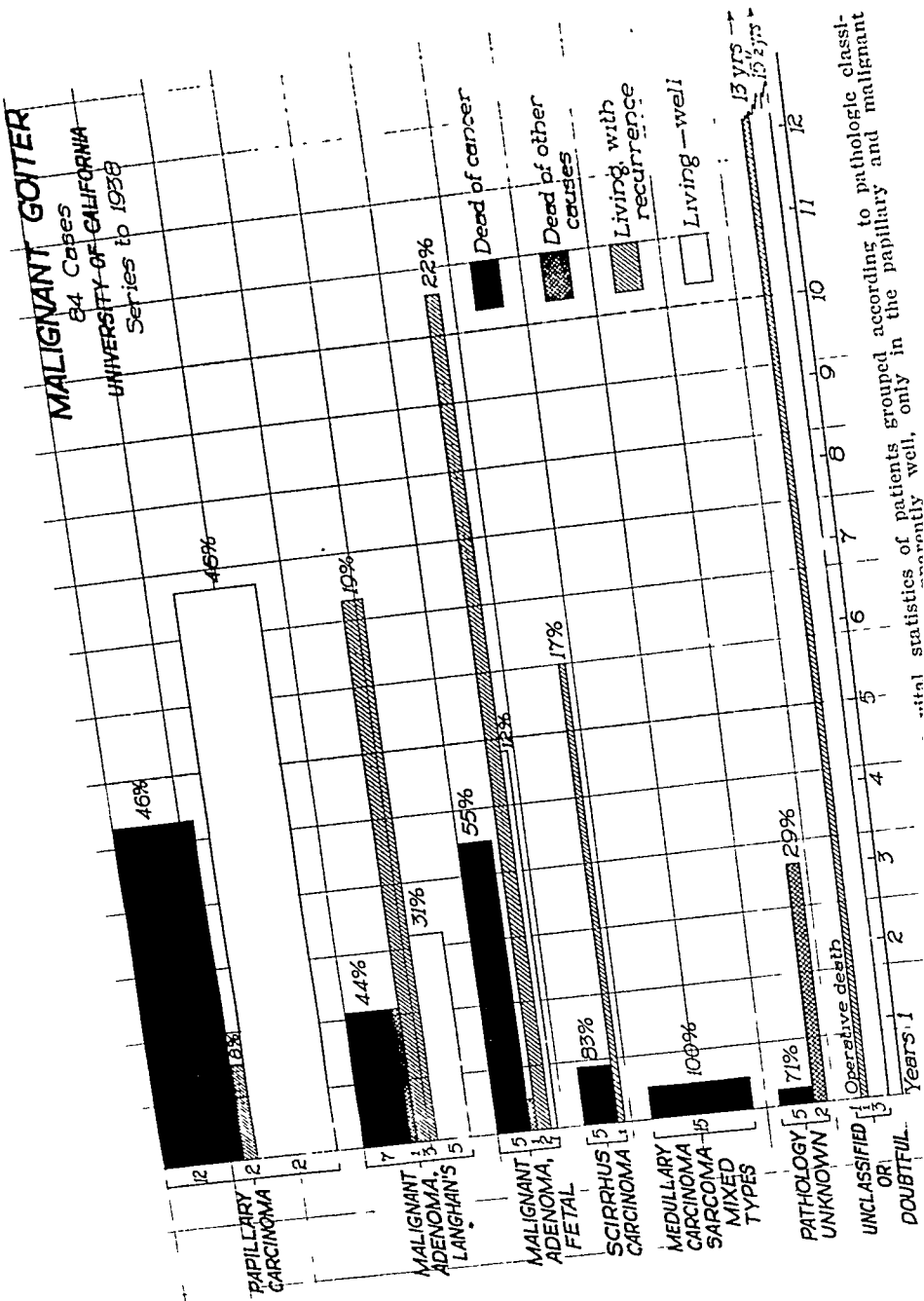
C.

B.

A.

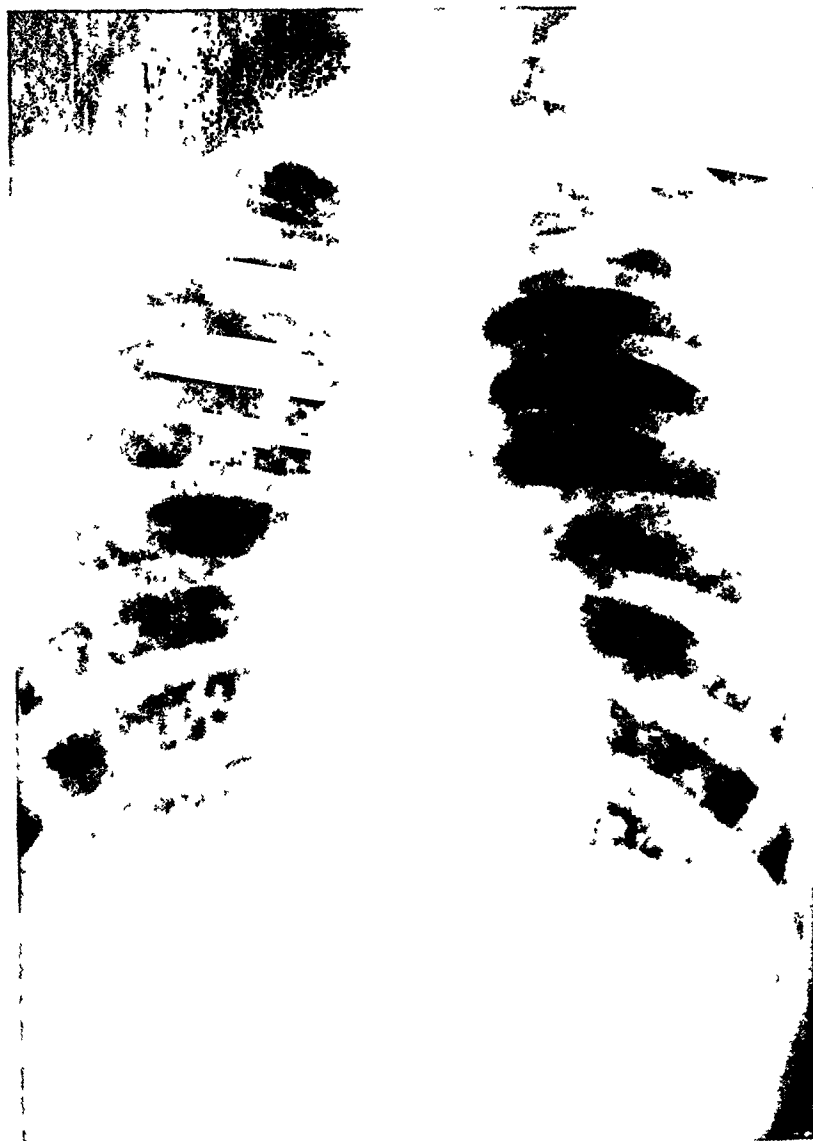
Fig. 5.—Three tumors of Group III, hopeless malignancy. A ( $\times 450$ ) is a small-cell carcinoma from a patient (Case 16) in whom thyroid alveoli are infiltrated and destroyed by small round cells. B ( $\times 450$ ) is from the patient in Case 65, large-cell carcinoma, showing leucocytic infiltration, a bad prognostic sign. Calcification, as shown in Fig. 24, was present in specimen from which B was taken. C ( $\times 120$ ) shows sarcomatous degeneration. Average length of life of the three patients illustrated was less than one year.

## WARD: MALIGNANT GOITER





operation on penetration of the capsule of the adenoma, and diagnosis in the laboratory only on minute gross and microscopic examination of the excised goiter tissue.



A

Fig 7—Roentgenograms (A and B) of chest of 9-year-old boy (Case 42) whose chest films show a similar picture now at age 22 and who has developed laryngeal paralysis and local recurrence only recently thirteen years after operation and irradiation. Microphotograph of tumor from this patient is shown in Fig 4 E.

The second cardinal point in prognosis, the pathologic pattern of the tumor, is well illustrated in the chart shown in Fig 6. Although this compilation was founded upon eighty-four cases studied to 1938, a similar trend has been shown since that time in double the number of cases.

The presence of a papillary pattern is so significant that, as previously indicated,<sup>15</sup> the degree of malignancy apparently can be estimated for a given tumor by the extent of its departure from this pattern; the greater the extent of departure, the more malignant the tumor. The explanation for this phenomenon is twofold: papillary tumors do not tend to



B.

Fig 7B (For legend see opposite page.)

invade blood vessels, and are thus filtered through the cervical lymphatics; in the series under discussion at least, papillary tumors have been more responsive to irradiation than the more cellular, anaplastic and undifferentiated growths.

The third prognostic point, metastasis, has a value similar to that in malignancy of other organs. The eventual outlook is poor in any case in which distant metastases have taken place. It should be remembered, however, that occasionally metastasis to the lung will lie dormant for many years after removal of the primary tumor. One patient in this series is in apparent good health thirteen years after the lungs were found to be riddled with miliary nodules (Fig. 7). Another has responded well to radiation therapy of pulmonary metastases, and is alive and well three years after operation.

Another feature peculiar to metastasis from the thyroid gland is the not infrequent occurrence of misnamed benign metastasizing goiter.

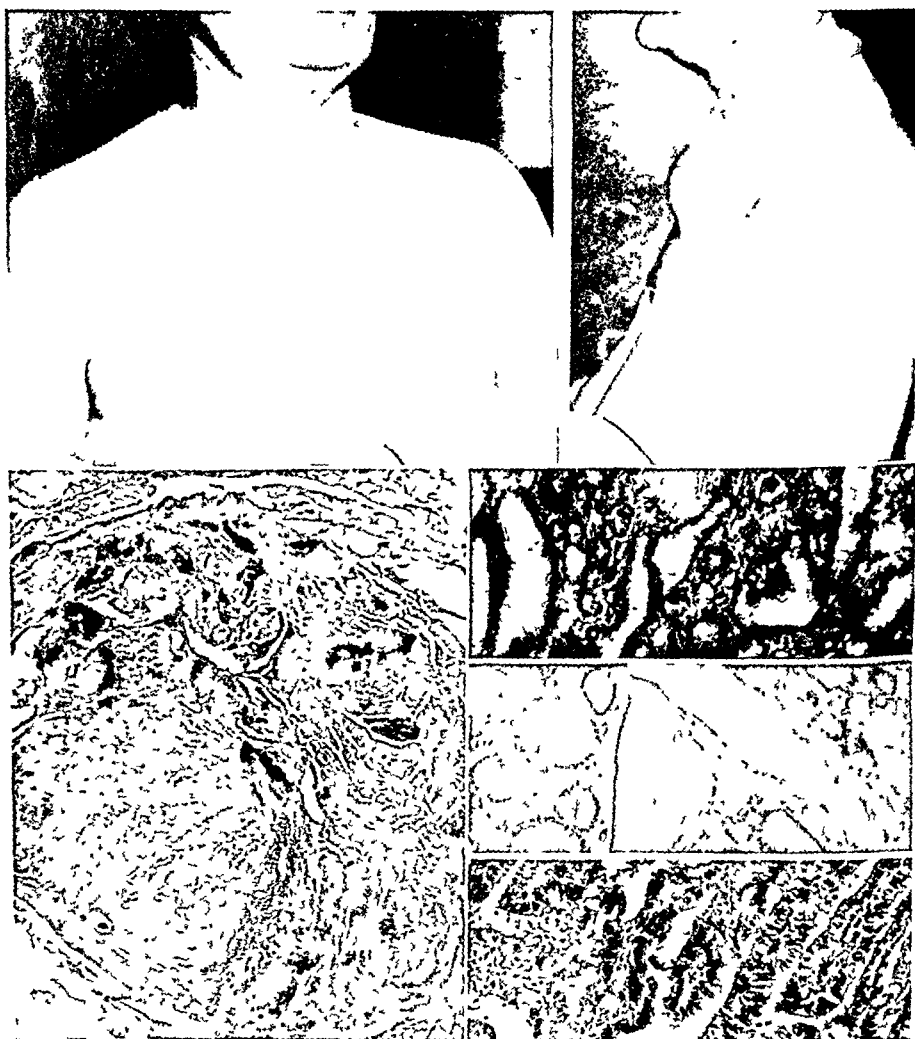


Fig 8—Malignant goiter (Case 118) primary lesion of which was discovered only after removal of clavicular tumor had shown it to be of thyroid origin. A and B show original clavicular tumor. C ( $\times 30$ ) entire primary tumor of left lobe of thyroid gland. D and E ( $\times 120$ ) sections of growth from clavicle. F ( $\times 120$ ), section of primary tumor.

The thyroid origin of many metastatic tumors found in bone is recognized only on pathologic examination of the involved section of bone. Like other observers, we have seen a number of these patients who had lived in apparent good health for many years after removal of an isolated metastatic nodule and later thyroidectomy. In some cases the primary lesion is microscopic, and is discovered only by serial section of the entire thyroid gland. Fig. 8 illustrates such a case.

#### TREATMENT

The discussion of treatment is conveniently divided into three parts, depending upon the stage in which the disease is seen. These stages are prophylactic, definitive, and palliative. Prophylactic treatment consists of the removal of nodular goiters so early that there is no preoperative suspicion of malignant change. For many years surgeons of experience have advocated extirpation of nodular goiters to avoid the danger of malignant degeneration. The statistics in this series (1 carcinoma in 9 men and 1 in 21 women operated on for nodular goiter) amply justify such a plan. This, in my opinion, provides abundant support for the recommendation of an operative procedure which carries as low a mortality and morbidity rate as thyroidectomy. The presence of a solitary adenoma in the thyroid, the finding of lateral masses which could be aberrant thyroid tissue, or the history of onset of rapid growth in a previously quiescent nodular goiter makes such a recommendation urgent. In my experience it has been rare to care for a patient with malignant goiter who has not been told at some time by a physician that the goiter was nontoxic and harmless, and that nothing should be done about it until signs of trouble appeared.

The operation carried out under the heading of prophylaxis varies with the experience of the surgeon and his knowledge of gross pathology. The enucleation of adenomas has been advocated and practiced by surgeons of experience for years. It is a relatively simple procedure, and is highly effective as a prophylactic measure. There have been times, however, when the pathologist has returned a report of malignancy, previously unsuspected, which caused me to regret that I had not performed a lobectomy or a subtotal thyroidectomy. In selected instances of this kind, the surgeon is justified in an immediate reoperation to remove the involved lobe and suspected soft tissue in the neighborhood. There are at least two patients in this series who have remained well for over fifteen years after such a procedure. In one, carcinoma was demonstrated in the specimen removed at the second operation; in the other, none was found.

Any operation for the removal of adenomatous nodules should include a thorough exploration by palpation of the uninvolved lobe, and an exploratory incision into that lobe if any doubt exists concerning the presence of nodules. The operation is incomplete if a single encapsulated nodule is allowed to remain.

If carcinoma is suspected before operation, radical removal of the involved tissue should be planned. A long collar incision should be made, slightly higher than customary. It is occasionally advisable to extend one end of the incision upward, in hockey stick fashion, to facilitate removal of submandibular extensions. The ribbon muscles should always be transected and, if infiltrated by tumor tissue, excised, a procedure which does not militate against a good functional or cosmetic result. The operation should be extensive enough to remove all involved structures and yet preserve at least one recurrent nerve, one parathyroid gland, and both carotid arteries. Crile and Crile<sup>3</sup> described a satisfactory technique for such an operation. If removal necessitates the sacrifice of one recurrent nerve this should be done, provided that pre-operative examination showed the other to be functioning. The use of an intratracheal catheter with an inflatable cuff, regardless of the type of anesthesia employed, is of great advantage. This prevents the collapse of a trachea softened by pressure or infiltration, and aids oxygenation during the operation.

When the lateral or inferior veins are found to be thrombosed by tumor tissue, ligation and resection of the internal jugulars should be attempted. Tumor invading the trachea should be excised flush with the tracheal wall either with the scalpel or the electric knife, and the base should be lightly coagulated. Special care must be taken to prevent injury to the esophagus, which may be adherent to the retrotracheal portion of the tumor.

Mediastinal extension of malignant tissue often proves to be the unsurmountable obstacle to complete removal of the tumor. If the growth is hard in consistency and of the infiltrating type, little can be done to excise the substernal portion even by splitting the sternum. If, on the other hand, the mediastinal portion consists of more or less encapsulated nodules, there are two methods of manipulation which may accomplish removal. The first of these is the operation described by Lahey<sup>10</sup> for ablation of substernal adenoma. In this procedure, the suprasternal portions of the tumor are freed from their bed and from the trachea, and are used to pull the mediastinal masses into the neck. The second method can be employed for many of the softer papillary growths and for those in which central degeneration of a nodule permits rupture of the pseudocapsule. In such a case, it may be possible to evacuate the mushy contents by curette or suction and collapse the capsule, thus permitting extracapsular finger dissection from the superior mediastinum.

After removal of the tumor, it is advisable to lavage with plain sterile water instead of saline solution because of the lytic effect of the former on possible free cancer cells. Lavage before closure reveals possible sources of bleeding and removes cellular debris, deposit of which is almost unavoidable in manipulation of the more friable tumors.

## RADIATION THERAPY

Roentgen therapy can be used alone for palliation or combined with surgery in an attempt to eradicate the disease. Even in advanced cases, a biopsy should be performed before irradiation is carried out. This offers the dual advantage of establishing the diagnosis and preventing irradiation of a pure papillary tumor, which may break down and ulcerate because of its extreme radiosensitivity. Since treatment of the patient shown in Fig. 9, even large, bulky papillary tumors have been surgically removed, followed by adequate postoperative radiation therapy in the hope of obtaining a cure. This patient died six weeks later of empyema secondary to tearing of the pleural apex at operation. Autopsy examination revealed no malignant tissue.

The principal value of x-ray therapy lies in its administration post-operatively, directed to the elimination of cancerous tissue not detected or not removable at operation. Such tissue is frequently located in the mediastinum, and for this reason the mediastinal space should be included in the area treated. Three thousand roentgens delivered to the tumor bed are considered to be the lower limit of effective dosage. The aim is to administer a dose sufficient to kill cancer cells, but not to exceed the tolerance of normal tissues in the irradiated zone. The best results can be expected to occur in tumors shown to be predominantly papillary in design. This has been substantiated in our series, and in Portmann's<sup>11</sup> studies 92 per cent of patients with papillary carcinoma survived more than five years. Not only are a greater number of apparent cures obtained by combined surgery and irradiation in the papillary group, but when recurrence does take place these tumors are more responsive and remain susceptible to radiation therapy for a longer period of time. It must be remembered, as Haagensen<sup>8</sup> pointed out, that sensitivity to irradiation should be judged from two aspects: the immediate response as shown by regression of the tumor, and the duration of that response. In both these respects, papillary tumors are the most susceptible to irradiation.

Other than for the papillary carcinomas, we have found little evidence that radiation therapy is of value except in a rather small number of malignant adenomas. It is, however, extremely difficult to estimate precisely the value of radiation therapy. When it is employed after operation, and the patient remains well and without recurrence, it is impossible to state whether the favorable result is due to the completeness of operative removal or to irradiation. Only when a tumor recurs and regresses or becomes dormant under a course of radiation therapy can the successful outcome be attributed wholly to this form of treatment. In the papillary group, a fair number of such cases has been followed for many years, a less number in the group comprised of Langhans' malignant adenoma, and very few in the fetal types of malignant adenoma. No case of anaplastic, large and small cell carcinoma, or car-



Fig. 9.—Patient (Case 41) before and after radiation therapy. Left column (A, B, and C) including microphotograph ( $\times 120$ ), represents condition before roentgen therapy. Right column (D, E, and F), shows condition shortly after completion of treatment; microphotograph ( $\times 80$ ).

cinoma has shown a favorable response to surgery or to irradiation (Fig. 6). It should be emphasized that surgery and irradiation are directed toward accomplishment of the same result—eradication of the growth. They are not antagonistic, but complementary, to each other. The most favorable results are to be anticipated when irradiation follows surgery; but occasionally x-ray therapy before operation makes surgical removal possible. In such cases, operation should be followed by adequate roentgen therapy.

#### TREATMENT OF RECURRENCE AND METASTASIS

The results of treatment of locally recurrent tumors and metastatic deposits are influenced even more strongly by the pathologic pattern of the growth than are the results of treatment of primary neoplasms. If the metastases are from a well-differentiated tumor, especially if it is predominantly papilliferous, their response to irradiation is usually good. If, on the other hand, they are of the usual blood-borne variety, malignant adenoma Langhans, they have in my experience shown little response to radiation therapy. Regardless of the pattern of the parent tumor, it is wise to give the patient a trial of irradiation if the metastatic lesions are not too widespread and fulminating.

Local recurrent nodules, especially if the primary growth was a malignant adenoma, should be removed. Graham<sup>7</sup> demonstrated that many of these cervical masses are tumor thrombi, often encapsulated in the lateral or inferior thyroid veins. Their removal by operation is especially indicated because of their lack of response to irradiation, and because years may intervene before they metastasize or recur again locally.

#### SUMMARY

1. Almost all malignant goiters are nodular. Carcinoma occurs so rarely in diffuse toxic goiter (1 in 168 malignancies in our series), that this group can be excluded from consideration.

2. The incidence of malignant goiter is influenced by the degree of endemicity and the frequency of nodular goiter in a given geographical locality.

3. Age groups of patients with carcinoma of the thyroid are similar to those of patients affected by this lesion in other organs, except that malignancy appears in aberrant thyroid tissue earlier in life.

4. The preponderance of malignant goiter is in favor of women; but the expectancy for carcinoma in men with nodular goiter is much greater—1 in 9 men (11 per cent) coming to surgery.

5. Of the three cardinal signs of malignant goiter: hoarseness, fixation, and hardness, at least the first two denote a far-advanced lesion. Any or all of these signs, however, can be produced by benign growths. Carcinomatous and calcareous degeneration may occur in the same nodule, and delay in removing it alters the prognosis unfavorably.



6. Long-standing or slowly growing tumors which suddenly undergo rapid growth and produce pressure symptoms are suspicious and should be extirpated before the clinical picture of malignancy develops.

7. We have found it practical from a prognostic and therapeutic standpoint to classify malignant thyroid tumors according to their characteristics of growth and their microscopic architecture. Table II shows our three groups: papillary carcinomas, malignant adenomas, and all others.

8. Prognosis is based on the time of diagnosis, the pathologic pattern, and the presence of metastasis. Deaths are in direct proportion to the ease of diagnosis. Papillary carcinoma offers the best prognosis, and the degree of malignancy can apparently be estimated by the corresponding extent of departure from the papillary pattern. The prognostic evaluation of metastasis is similar to that in carcinoma of other organs, with the exception of rare dormant metastatic lesions in patients seemingly well years after operation and irradiation.

9. Prophylaxis consists of the removal of nodular goiters so early that there is no preoperative suspicion of malignant change. Our statistics of 1 carcinoma in 9 men and 1 in 21 women operated on for nodular goiter substantiate the importance of this procedure. Suspected or diagnosed carcinoma calls for radical resection, always preserving at least one recurrent nerve, one parathyroid gland, and both carotid arteries.

10. Roentgen therapy can be used alone or in combination with surgery, but should never be administered without the benefit of a biopsy report. Results may be expected to be good in the extremely radiosensitive papillary carcinomas, fair in a small number of malignant adenomas, and unfavorable in all others. The principal value of x-ray therapy lies in its administration postoperatively.

11. Locally recurrent tumors and metastatic deposits are treated depending on their pathologic pattern. Trial irradiation is justified, regardless of the pattern of the primary tumor, if the metastatic lesions are not too widespread and fulminating. Locally recurrent nodules should be surgically removed.

12. Statistics concerning the different types of goiter treated at the University of California Hospital through 1943 are presented, 5,439 cases being reviewed. Of these, 3,539 goiters were nodular, and 168 malignant (4.8 per cent). Living after five years were 20 per cent of the patients in whom carcinoma was diagnosed or suspected before operation, 40 per cent in whom carcinoma was diagnosed at operation, and 80 per cent in whom it was diagnosed first on pathologic examination.

#### REFERENCES

1. Broders, A. C.: *Regenerative Hyperplasia in Exophthalmic Goiter; Condition Simulating Carcinoma*, Virginia M. Monthly 56: 453-456, 1929.
2. Clute, H. M., and Warren, S.: *Prognosis of Thyroid Cancer*, Surg., Gynec. & Obst. 60: 861-874, 1935.

3. Crile, G., and Crile, G., Jr.: Radical Operation for Malignant Tumors of Thyroid Gland, Surg., Gynec. & Obst. 64: 927-934, 1937.
4. Davis, A. C.: Paralysis of Vocal Cord, Tr. Am. A. Study Goiter, pp. 95-104, 1941.
5. Eberts, E. M., Fitzgerald, R. R., and Silver, P. G.: Surgical Diseases of Thyroid Gland, Philadelphia, 1929, Lea & Febiger, p. 214.
6. Graham, A.: Malignant Epithelial Tumors of Thyroid, Surg., Gynec. & Obst. 39: 781-790, 1924; Malignant Tumors of Thyroid, Epithelial Types, Ann. Surg. 82: 30-44, 1925.
7. Graham, A.: Malignant Adenoma of Thyroid; Local Recurrences in Veins of Neck, Surg., Gynec. & Obst. 66: 577-590, 1938.
8. Haagensen, C. D.: Cancer of Thyroid: Its Radiosensitivity, Am. J. Cancer (supp.) 15: 2063-2105, 1931.
9. Kocher, T.: Zur klinische Beurteilung der bösartigen Geschwülste der Schilddrüse, Deutsche Ztschr. f. Chir. 91: 197-307, 1907.
10. Lahey, F. H.: Surgical Management of Intrathoracic Goiter, Surg., Gynec. & Obst. 53: 346-354, 1931.
11. Portmann, U. V.: Experiences in Treatment of Malignant Tumors of Thyroid Gland, Am. J. Roentgenol. 46: 454-466, 1941.
12. de Quervain, F.: Zur Kenntnis der wuchernden Struma nach Langhans. Verhandlungsbericht der zweiten Internationalen Kropfkongferenz (1933). Bern, 1935, Hans Huber, pp. 650-675.
13. Ward, R., and Carr, J. L.: Malignant Goiter. Statistical Study of 36 Cases, Tr. Am. A. Study Goiter, pp. 122-125, 1930.
14. Ward, R.: Malignant Goiter; Survey of Geographical Types, West. J. Surg. 43: 494-504, 1935.
15. Ward, R.: Prognosis of Malignant Goiter in Relation to Pathologic Types, West. J. Surg. 47: 437-448, 1939.
16. Ward, R.: Relation of Tumors of Lateral Aberrant Thyroid Tissue to Malignant Disease of Thyroid Gland, Arch. Surg. 40: 606-645, 1940.
17. Wegelin, C.: Malignant Disease of Thyroid Gland and Its Relation to Goitre in Man and Animals, Cancer Rev. 3: 297-313, 1928.
18. Wilson, L. B.: Malignant Tumors of Thyroid, Ann. Surg. 74: 129-384, 1921.

## PARATHYROID TETANY

CYRIL M. MACBRYDE, M.D., ST. LOUIS, MO.

*(From the Department of Internal Medicine, Washington University School of Medicine, the Barnes Hospital and the Washington University Clinics)*

**I**MPROVEMENT in surgical technique has resulted in a steady diminution of the incidence of parathyroid deficiency following operations upon the thyroid gland. The parathyroid glands may be inadvertently removed, or their blood supply may be interfered with by ligation during operation, or by thrombosis or fibrosis occurring later. Tetany from fibrosis usually appears several weeks postoperatively. Occasionally edema in the immediate postoperative period seems to curtail temporarily the blood supply of the parathyroids, for postoperative tetany may be transient, disappearing as the edema subsides.

Despite the fact that modern surgery has reduced its incidence in large clinics to figures ranging from 1.5 to 0.5 per cent,<sup>1</sup> it is likely that the total number of cases has actually increased because of the increasing frequency of operations upon the thyroid and parathyroid glands. Preservation of the posterior thyroid capsule and the principle of subtotal thyroidectomy, with a better understanding of the usual anatomic location and frequent aberration of the four parathyroid glandules, will permit further reduction in postoperative hypoparathyroidism. When a second or third operation is performed the hazards to the parathyroids are, of course, greatly increased. When the parathyroid glands are seriously damaged or removed at operation, tetany may appear within twenty-four hours.

Spontaneous hypoparathyroidism is rare. The clinical state known as idiopathic tetany results, and is similar in all respects to that produced by surgical damage to the glands. Apparently idiopathic tetany was not always so uncommon as it is at present, for large numbers of cases were reported in central Europe toward the end of the last century, particularly in Vienna. In that city between 1880 and 1895 there were 368 cases studied in the General Hospital, the majority of the patients being young cobblers or tailors. The fact that the greatest frequency of onset occurred in the late winter and in these indoor sedentary workers suggests vitamin D deficit as the cause. Infantile tetany or spasmophilia is another condition now seen relatively infrequently. It is apt to occur in babies who have been fed cows' milk instead of human milk. Erdheim believed that it must result from parathyroid insufficiency, since autopsy frequently revealed hemorrhage into these glands. However, in many cases vitamin D deficiency

and poor calcium intake or absorption seem to play the major role. Here again the incidence is greatest in late winter. In pregnancy and lactation tetany may appear, and may result from a latent hypoparathyroidism which becomes apparent only after there has been a great and prolonged drain upon the maternal calcium stores. Osteomalacia is apt to be present in these women. Similarly, the bone defect known as rickets frequently is present with infantile tetany. It seems likely that in these so-called idiopathic or functional hypoparathyroid states the chain of events may be as follows: first there is a prolonged deficit of vitamin D or of calcium, or both, and in consequence, the parathyroid glands are called upon to secrete an additional amount of hormone to sustain the falling blood calcium. The glands may hypertrophy, and the demand may be successfully met. (Hypertrophy and hyperplasia of the parathyroids are frequent findings in rickets.) If there is an inherent weakness of the glands, or if function eventually fails after prolonged excessive demands, tetany results.

*Signs and Symptoms.*—When the serum calcium is between 4 and 6 mg. per cent symptoms are usually manifest. Muscular spasm occurs, particularly carpopedal spasm. The facial and abdominal muscles may be thrown into violent contractions by the mildest stimuli. Painful paroxysms may occur spontaneously. Numbness and tingling of face, hands, feet, and legs may be constant. Epileptiform convulsions may occur and in some cases papilledema is present, suggesting intracranial tumor.<sup>2</sup>

When the blood calcium is 7 or 8 mg. per cent the condition is usually latent. Excitement, exertion, overbreathing, or menstruation may provoke an attack. When the tetany is of long duration ectodermal changes occur, the most serious of which is the formation of bilateral cataracts. The hair becomes lifeless and brittle and thins considerably. Nails become ridged, and teeth, especially in growing patients, become ridged and grooved horizontally. Gastrointestinal disturbances are common with abdominal pain, "gas," and alternating constipation and diarrhea. The least pressure on arm or leg may cause cramping. Rapid motion may become impossible without resulting in painful muscular spasm.

*Pathologic Physiology.*—All true tetany occurs as the result of the presence of insufficient amounts of ionized calcium in the blood. Any condition which decreases the amount of calcium absorbed or which increases the pH of the blood may result in tetany. The total blood calcium may be low, or only the ionized fraction may be subnormal. The effect in either case is to decrease the regulating, inhibitory effect of ionized calcium upon neuromuscular irritability. Phosphate metabolism is closely associated with calcium metabolism and a rise in the blood phosphate is quite regularly accompanied by a fall in the blood calcium, perhaps because there is induced a deposit of calcium and

phosphate in chemical combination. The following clinical forms of tetany have been recognized:

1. Parathyroid insufficiency, postoperative and spontaneous. The parathyroid hormone increases calcium absorption from bone and increases the proportion of ionized calcium in the blood. Hormone lack causes tetany.
2. Calcium starvation: inadequate calcium intake.
3. Poor calcium absorption, occurring with low vitamin D intake, with steatorrhea, and in conditions in which inadequate amounts of bile reach the intestine, calcium soaps being formed and excreted.
4. Calcium depletion: pregnancy, lactation.
5. Alkalosis
  - (a) from vomiting, with loss of HCl
  - (b) from excessive ingestion of alkaline salts such as sodium bicarbonate
  - (c) from overbreathing, with loss of  $\text{CO}_2$
6. Excessive phosphate intake, or excessive phosphate retention with hyperphosphatemia, for example, the tetany occurring with "renal rickets."

*Diagnosis.*—The diagnosis depends upon the recognition of the symptoms and signs, which are usually quite characteristic. Confirmatory evidence may be secured through three signs when the tetany is latent or only manifest at intervals: Erb's, Chvostek's, and Trousseau's signs. Erb's sign consists in the production of muscular contraction with the stimulating electrode over a motor nerve, the response being elicited by a much weaker galvanic electrical stimulus than is normally necessary. The cathodal opening response is obtained with less than 5 ma., while normally over 6 ma. are required. Chvostek's sign consists in a contraction of the innervated muscles in response to gentle tapping over the trunk of the facial nerve just anterior to the external auditory meatus. Trousseau's sign depends upon the temporary deprivation of the blood supply to a nerve trunk, either by direct pressure on the nerve, or by application of a pressure cuff to an extremity. When the blood pressure cuff is applied above the elbow and inflated the typical carpal spasm will occur within one to three minutes. All of these signs depend upon increased irritability of the nerves.

When tetany is due to alkalosis, the total serum calcium level is usually normal. The blood calcium may be low in conditions associated with poor calcium or vitamin D intake or absorption. In hypoparathyroidism the serum calcium may be very low, the lowest levels of 4 to 6 mg. per cent occurring usually in manifest tetany. With levels of 7 or 8 mg. per cent the tetany is apt to be latent. In parathyroid tetany the inorganic phosphate is usually elevated from the

normal of 3 or 4 mg. per cent to 6 or 8 or even 10 mg. per cent. Normal or low blood phosphate may occur in nutritional hypocalcemia. Blood phosphate may rise with severe kidney damage, with consequent fall in the serum calcium and production of tetany.

*Treatment.*—The proper therapy of tetany will, of course, depend upon its etiology. Correction of alkalosis by prevention of overbreathing, or by ingestion of ammonium chloride or dilute hydrochloric acid may be indicated. Restoration of adequate calcium and vitamin D intake, and measures to promote their absorption, are necessary when the calcium metabolism derangement lies in this sphere.

We are here primarily concerned with parathyroid tetany. Treatment of hypoparathyroidism may be considered under two headings: the acute attack and chronic tetany.

1. *The Acute Attack:* A patient may die in a severe attack, from spasm of the glottis, or of the diaphragm, or from repeated epileptiform convulsions. Prompt and vigorous intervention is necessary. The most effective measures are (and they should be given in this order):

(a) *Intravenous calcium.*—Calcium chloride is the most effective measure because of its high calcium content and its acid, highly ionized state. It is, however, highly irritating to tissues, and will cause necrosis if leakage occurs outside the vein. From 10 to 20 c.c. of a 5 per cent solution will cause abrupt termination of most attacks. Less irritating to tissues is calcium gluconate, which may be given intravenously (or deep intramuscularly into the buttock, if intravenous injection is not feasible) in doses of 10 or 20 c.c. of 10 per cent solution. Although the blood calcium is restored to normal promptly, relief will be only transient in severe tetany. The serum calcium will fall within one to four hours to its previous level as a rule. The intravenous injection may be repeated once or twice if necessary until the effect of the second therapeutic measure becomes evident.

(b) *Parathyroid extract.*—One to three cubic centimeters of parathyroid hormone (100 U.S.P. units per cubic centimeter) should be given intravenously or intramuscularly immediately after the intravenous calcium is administered. The effect upon the serum calcium is evident in a few hours, the peak effect usually occurring in from eight to eighteen hours, while in from twenty to twenty-four hours all effect is lost. Therefore, the hormone will usually be giving a good response just about the time the effect of the one or two intravenous calcium injections is wearing off. To maintain an approximately normal blood calcium in a patient with severe hypoparathyroidism requires daily injections of the extract. This is expensive and unpleasant. Furthermore, a tolerance is usually developed, larger and larger doses are required, and finally little or no response occurs. Maintenance treatment of chronic tetany formerly consisted of high calcium intake plus daily hormone injection, but fortunately better methods have been developed.

Another possible means of supplying hormone is the implantation of parathyroid tissue. In our experience such transplants have been ineffective, even when performed after preliminary culture of the parathyroid tissue in the recipient's serum, as advocated by Stone, Owings, and Gey.<sup>3</sup> Even after the procedure was repeated four times at intervals of some months in one of these cases, no definite results were observed. In one patient only temporary benefit was obtained from a parathyroid transplant obtained from her mother.

2. *Chronic Tetany*: The treatment of chronic tetany should begin as soon as it is evident that the patient cannot maintain a normal serum calcium level. The effective measures are:

(a) *High calcium intake*.—A quart of milk will supply approximately 1 Gm. of calcium daily, and, in addition, from 10 to 15 Gm. of calcium lactate or gluconate are usually advisable. This is best taken as two to four teaspoonfuls well stirred in hot water or milk, distributed throughout the day. It is not necessary to limit phosphorus intake, but a high phosphorus diet is undesirable, which means primarily that meat and protein foods should be eaten only in normal amounts.

(b) *Desiccated thyroid*.—Desiccated thyroid promotes calcium absorption and helps maintain a normal serum calcium when hypothyroidism as well as hypoparathyroidism is present. The dose needed varies from 1 to 3 gr. daily, enough being given to restore the basal metabolic rate to normal.

(c) *Dihydrotachysterol* (Hytakerol, Winthrop\*).—Dihydrotachysterol can be taken orally in capsules each containing 0.625 mg., and will maintain serum calcium within normal limits in even the most severe cases of hypoparathyroidism.<sup>4</sup> The dose varies with the severity of the case and with the amount of calcium ingested. With higher doses of calcium, smaller doses of dihydrotachysterol are possible. Among fourteen patients we have studied with severe chronic hypoparathyroidism, the requirement is either one or two capsules daily when between 10 and 15 Gm. of calcium lactate powder are taken. In four of the more severe cases the patients need two capsules and 15 Gm. of calcium lactate per day; four patients require one capsule only with the same calcium intake. Of the remaining six patients, three take one capsule and approximately 15 Gm., and three take one capsule and 10 Gm. Twelve of the patients had postoperative tetany, eleven after thyroid operations, one after removal of a parathyroid tumor. Two had idiopathic hypoparathyroidism.

Enough dihydrotachysterol can be given to raise serum calcium to normal even if calcium intake does not exceed that in the normal diet. The amounts of calcium used in this series of patients have not caused

\*The dihydrotachysterol for these studies was furnished by the Medical Research Department of the Winthrop Chemical Company, Inc.

digestive upsets, are not particularly disagreeable, and make the treatment much less expensive. From two to four capsules per day are necessary with a normal calcium intake.

The rise in blood calcium is more rapid if larger doses of dihydrotachysterol are given for the first few days and the maintenance dose is adopted when the serum calcium level approaches normal. A good dosage scheme for a patient with a serum calcium of 6 mg., given 15 Gm. of calcium lactate daily, might be one capsule four times daily the first three days, then two capsules per day until the serum calcium reaches 9 or 10 mg. The dose can be reduced to one capsule if the serum calcium exceeds 10 mg., or in a mild case one capsule every other day may suffice. With this dosage scheme a normal serum calcium should be reached in from seven to ten days. The first rise is often not evident for forty-eight hours. When the drug is stopped, the blood calcium falls slowly over a period of two or three weeks. The advantages of dihydrotachysterol over parathyroid extract in the treatment of chronic parathyroid insufficiency are:

1. The action is more prolonged
2. It is effective when taken orally
3. No tolerance is developed
4. It is less expensive
5. It is stable and retains its potency when kept at ordinary room temperatures

Dihydrotachysterol in excessive amounts can cause hypercalcemia and severe toxic effects. Frequent determinations of the blood calcium are necessary until the maintenance dose is established, then the serum calcium need be measured only every two or three months.

(d) *Vitamin D*.—Various forms of vitamin D are effective in raising serum calcium. Doses of from 150,000 to 400,000 U.S.P. units daily plus a fortified calcium intake of 3 Gm. of calcium chloride (as 25 per cent solution in syrup of glycyrrhiza) gave good results in a series of six cases studied by Sevringhaus and St. John.<sup>5</sup>

In comparative studies on eight of the fourteen patients in our series we found that vitamin D<sub>2</sub> (calciferol\*) gave results similar to those obtained with dihydrotachysterol. Vitamin D seemed to have less effect in promoting phosphorous excretion. Serum phosphate levels tended to be somewhat higher than with dihydrotachysterol. We employed doses of 100,000 units (two capsules) daily in most of our cases, and found this sufficient if from 5 to 15 Gm. of calcium lactate or gluconate were given. The same dangers of hypercalcemia with cumulative effects must be guarded against with vitamin D as with dihydrotachysterol. When the serum calcium was maintained within normal limits, patients felt equally well with the two drugs.

\*In the form of Drisdol (Winthrop) 50,000 U.S.P. units per capsule.



## SUMMARY

Spontaneous idiopathic tetany and spasmodophilia are relatively rare, while postoperative tetany is less frequent as surgical technique improves.

Acute severe tetany demands immediate recognition and treatment. A patient complaining of numbness, tingling, or cramps after a thyroid or parathyroid operation should have a venipuncture with withdrawal of blood for serum calcium determination, then intravenous calcium should be given, and intramuscular parathyroid extract. Should symptoms of tetany persist for several days, treatment with high calcium intake and dihydrotachysterol or vitamin D should be instituted. Chronic tetany is a severe illness causing much discomfort and disability as well as late trophic changes such as cataracts. Good treatment now relieves patients of all such symptoms and prevents the trophic changes.

## REFERENCES

1. Swinton, N. W.: Postoperative Parathyroid Tetany, *New England J. Med.* 217: 165, 1937.
2. Barr, D. P., MacBryde, C. M., and Sanders, T. E.: Tetany With Increased Intracranial Pressure and Papilledema—Results From Treatment With Dihydrotachysterol, *Tr. A. Am. Physicians* 53: 227-232, 1938.
3. Stone, H. B., Owings, J. C., and Gey, G. O.: Living Grafts of Thyroid and Parathyroid Glands, *Surg., Gynec. & Obst.* 60: 390-393, 1935.
4. MacBryde, C. M.: The Treatment of Parathyroid Tetany With Dihydrotachysterol, *J. A. M. A.* 111: 304-307, 1938.
5. Sevringhaus, E. L., and St. John, Ruth: Parathyroid Tetany Treated With Massive Doses of Vitamin D, *J. Clin. Endocrinol.* 3: 635-637, 1943.

## Editorial

---

### Progress and Future in the Treatment of Goiter

TWO or three decades ago a succession of important discoveries in the field of goiter was announced. These included the isolation of thyroxin by Kendall (1914), prevention of goiter with iodine by Marine and Kimball (in the school children of Akron, 1921), the re-discovery of the beneficial effect of iodine in toxic goiter by Plummer (1923), and the production of thyroid hyperplasia by the thyrotropic hormone of the pituitary gland (Loeb and Bassett, 1929). These milestones of progress gave promise of solving the mystery of etiology of goiter and simplifying treatment with perhaps the elimination of surgical procedures; however, these accomplishments were not immediately forthcoming. Although valuable contributions have been made since these discoveries, none could be considered epochal until the inhibiting effect of thiouracil and thiourea was demonstrated by Astwood (1943), following the experimental work of Kennedy and Purves (1941) and others. The primary value of thiouracil, like iodine, is in preparation of the patient for operation. However, preliminary experiences of Astwood on prolonged treatment with thiouracil as reported in this symposium suggest that symptoms may not recur following discontinuance of the drug at least in some of the patients. The effect of thiouracil in neutralizing thyrotoxicosis is much more pronounced than iodine—so much so that postoperative crisis will probably be completely eradicated with its use. However, the relatively slow action of thiouracil may make it uneconomical to use in mildly toxic goiter where iodine preparation is entirely adequate and requires a much shorter period of preoperative therapy. Although the basic cause of toxic goiter remains undiscovered, it is now obvious that the serious aspects of the disease have been almost totally eliminated. The incidence of goiter has decreased in a few localities, at least. The report of Marine and Kimball revealed the efficacy of iodine (in the form of iodized salt) in the prevention of goiter (toxic as well as nontoxic) in school children of Akron. Although this work, with similar results, has been extended by Kimball (1938) in Michigan, the public health aspects have not been appreciated sufficiently for the use of iodized salt or equivalent iodine therapy to be adopted universally. Recently many clinicians have gained the impression that there is a definite decrease in the incidence of toxic goiter presumably based on the use of iodized salt. The writer was not convinced of this decrease in incidence in goiter in adults until recently, when the number of goiter patients was compared

to other admissions to Illinois Research Hospital. Fig. 1 illustrates the percentage of thyroid patients in the total admissions on the surgical service (adults) in Illinois Research Hospital. The average yearly incidence of thyroidectomies for goiter (inclusive of toxic diffuse, toxic nodular, and nontoxic nodular) in the total number of admissions on the surgical service for the three-year period of 1927, 1928, and 1929 was 19.3 per cent, whereas the average for the years 1941, 1942, and 1943 was 11.3 per cent of surgical admissions. During these two periods the number of thyroidectomies comprised 3 per cent and 1.9 per cent, respectively, of the total admissions (all services) to the hospital. This decrease in incidence is too great to be considered a coincidence; the

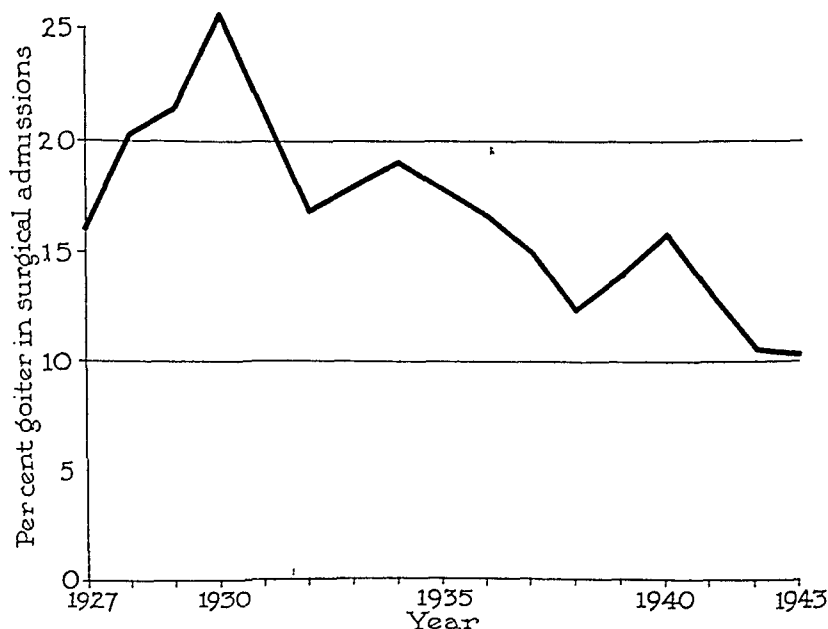


Fig. 1.—The curve illustrates the decline in incidence of goiter (thyroidectomy) in the total surgical admissions to Illinois Research Hospital.

use of iodized salt appears to be the best explanation of this decrease in goiter. The use of iodized salt\* in the Chicago area was begun in 1924. Naturally, it would take a few years for the iodine therapy to be reflected in the incidence of goiter. The drop in the incidence of goiter (operations) in the total surgical admissions, from 19.3 per cent to 11.3 per cent in the fourteen-year interval, can be explained better by the factor of increased iodine intake than by any other local factor known to the writer. The amount of iodized salt sold in 1924 after its introduction was estimated at 60 to 65 per cent. Of the total amount sold during the past few years this percentage has decreased slightly, being 58 per cent in 1943. The ratio of the various types of goiter has remained relatively unchanged, indicating that whatever the cause of the decrease in goiter

\*Data kindly supplied by the Morton Salt Company, Chicago.

of operable type, the various types have been affected equally. However, it must be emphasized that restoration of the proper iodine intake alone cannot be expected to eliminate goiter because goiter of all types still exists along the seaboard where iodine intake (particularly in drinking water) is presumably adequate. Moreover, the added intake of iodine in iodized salt in these communities during the past few years has not resulted in any decrease in goiter. As a matter of fact, in some communities (for example, New Orleans) the incidence of goiter appears to be on the increase.\*

Much difference of opinion exists as to whether or not excision of nontoxic nodular goiter is advisable. However, at least a great many surgeons advise removal because of the possible development of carcinoma, thyrotoxicosis, and pressure manifestations. After reviewing the incidence of carcinoma of the thyroid in nontoxic nodular goiters removed at Illinois Research Hospital, the author became convinced that removal of nontoxic nodular goiter should be advised almost routinely except in aged people or patients with complicating diseases. In general, the urgency is greater in young people, particularly if the nodule is solitary, largely because the incidence of carcinoma is highest in these two instances.

During the past several years the mortality rate following thyroidectomy has been lowered gradually until now it will probably average between 0.5 and 1.5 per cent in the various clinics where a large number of patients are cared for. There will be or should be a definite superiority of mortality rate in a series dealing with private cases over a series in a charity clinic for two reasons: (1) Private patients will come to the physician earlier, that is before cardiac and other organic damage is pronounced; and (2) for financial reasons the nutritional imbalance will be greater in the charity patient—a serious detriment in a disease which affects nutrition primarily. To maintain a commendable mortality rate the surgeon must be particularly cautious in his estimation of operability. This precaution is just as important in thyrotoxicosis as it is in other diseases such as carcinoma of the colon and stomach where nutritional depreciation is such a prominent factor. Although the experienced clinician may estimate operability quite accurately by a brief survey of the patient, he will nevertheless make fewer errors if he will adopt mathematical principles as much as possible; he will certainly have an enormous amount of difficulty in teaching methods of estimating operability to students unless he utilizes mathematical principles in his prerequisites.

Whatever the method adopted for estimating operability, there is one prerequisite which must never be broken, that is, bilateral thyroidectomy must never be performed in severe thyrotoxicosis unless the patient is showing a weight gain. In patients with doubtful operability, only one

\*Ochsner, Alton: Personal communication.

lobe should be removed at the first operation. An interval of at least three or four weeks should intervene before the second lobe is removed. Ligation of the superior thyroid artery has been abandoned as a stage operation.

Since thiouracil is so effective in neutralizing toxicity, the need for stage operations will unquestionably be markedly decreased. In spite of this tremendous advantage of thiouracil over iodine, it possesses two disadvantages, (1) the drug is occasionally toxic, and (2) a much longer interval is required to obtain reduction in the thyroid toxicity.

—*Warren H. Cole, M.D.*  
Chicago, Ill.

# SURGERY

VOL. 16

DECEMBER, 1944

No. 6

## Original Communications

### ESOPHAGEAL DUPLICATIONS OR MEDIASTINAL CYSTS OF ENTERIC ORIGIN

WILLIAM E. LADD, M.D.,\* AND H. WILLIAM SCOTT, JR., M.D.†  
BOSTON, MASS.

(From Department of Surgery, Harvard Medical School and Surgical Service,  
The Children's Hospital)

#### INTRODUCTION

IN THE last several years one of us (W. E. L.) has published reports concerning duplications of the alimentary tract and the surgical treatment of these "enterogenous cysts."<sup>1,2</sup> During this time five individuals with enterogenous cysts of the mediastinum, or better, "duplications of the esophagus," have been treated at The Children's Hospital. The unique problems presented by these lesions and their surgical management have prompted this report.

#### CASE REPORTS‡

CASE 1 (No. 173795).—D. S., a white boy, 22 months of age, one of six children, was admitted to the Children's Hospital Feb. 20, 1928. The family and past histories were noncontributory. The child had been well until two months before entry at which time he developed pneumonia on the right side, with a high fever for four days. The temperature then returned to normal and after two weeks in bed the patient was allowed up. During his illness he lost considerable weight.

Four days before entry the patient became ill with fever, dyspnea, and vomiting. After the first day the fever subsided but the vomiting continued. On the morning of entry the right ear began to discharge purulent material.

*Physical Examination.*—Temperature was 101° F., pulse 130, respirations 40 to 50, weight 21 pounds. The child was a pale, underdeveloped, and undernourished boy who could lie only on his right side because of marked dyspnea. There was a harsh, brassy cough. A purulent otitis media was present on the right side.

\*William E. Ladd Professor of Child Surgery, Harvard Medical School, Chief of Surgical Service, The Children's Hospital.

†Assistant in Surgery, Harvard Medical School and Junior Attending Surgeon, The Children's Hospital.

‡Cases 1 and 2 were reported previously by Ladd and Clifford<sup>1</sup> under the title of "Congenital Mediastinal Cysts of Enteric Origin." Since we now know them to be duplication of the esophagus we feel that it is justifiable to report these cases again with the title "Duplications of the Esophagus." Since we feel that it is justifiable to report these cases again with the title "Duplications of the Esophagus." Since we feel that it is justifiable to report these cases again with the title "Duplications of the Esophagus."

Received for publication, Oct. 11, 1944.

The chest was barrel-shaped with marked costal retraction and diminished expansion on the right side. The right base posteriorly was flat to percussion. Breath sounds were diminished over the whole right chest and absent below the angle of the scapula. A few moist râles were present over the right apex. Tactile fremitus was absent over the right side of the lower back with bronchial breathing over the right upper chest anteriorly. The heart was displaced  $2\frac{1}{2}$  cm. outside the left nipple line. The abdomen was protuberant and both spleen and liver were palpable 5 cm. below the costal margin. The fingers showed suggestive clubbing.

The roentgen examination suggested fluid, and a tentative diagnosis of empyema was made. Thoracentesis yielded 360 c.c. of a viscid, opalescent fluid. This was acid in reaction; its specific gravity 1.010; chloride 114 meq./l; bicarbonate 34 volume per cent; 560 cells per cubic millimeter with 80 per cent polymorphonuclears.



A.

Fig. 1 (Case 1, D. S.).—A, Sixteen years after successful operation for esophageal duplication. B, Roentgenogram of chest of same patient.

The withdrawal of the fluid afforded temporary relief of the symptoms. The diffuse clouding of the right chest by roentgenogram was replaced by a clear lateral lung field and a large, dense shadow running obliquely downward and outward from the hilus. Lipiodol bronchograms gave no diagnostic assistance, although the right upper bronchus failed to fill. The fluid rapidly reaccumulated and repeated tapplings were necessary. The child continued to run a low-grade temperature. In view of the character of the fluid and the roentgenologic findings, a diagnosis of intrathoracic cyst was made.

Exploratory thoracotomy was carried out under gas oxygen anesthesia on the twenty-second hospital day. The right upper lobe was atelectatic, rubbery, and yellowish red in color. The two lower lobes were only partially expanded and

displaced forward by a large, tense, smooth-walled cyst extending from the diaphragm to the apex of the thorax and filling the right paravertebral gutter. There were no adhesions within the pleural cavity. The cyst was estimated to fill two-thirds of the right thoracic cage. Anteriorly, it was covered by the visceral pleura which was reflected laterally onto the thoracic wall and mesially along the mediastinum, posterior to the root of the lung. In diameter it appeared to be about two and three-quarter inches at its diaphragmatic attachment,



B.

Fig. 1 B. (For legend see opposite page.)

which was retropleural. It was slightly smaller at the apical limit of the tumor, which was also covered by pleura. The condition of the child did not warrant excision of the cyst. Consequently its periphery was dissected free, the cyst wall sutured to the wound edges, and the chest wall closed around it in layers. Six days later the exteriorized cyst was opened and a catheter inserted for drainage. The latter procedure was followed by a very severe reaction with a high temperature. Four transfusions were given at intervals and there was gradual improvement. There were recurrent infections of the cyst cavity, however, with



elevation of temperature. There was no gain in weight, but the brassy cough ceased. Repeated roentgenograms with lipiodol injection into the marsupialized cyst demonstrated considerable diminution in size. There was a copious amount of clear, white, mucoid drainage which resembled gastric juice.

Four months after the marsupialization of the cyst an attempt at complete excision was carried out under gas-oxygen anesthesia. The old incision was reopened and the seventh rib resected. The cyst was found to be approximately one-half its former size. The wall was greatly thickened and fibrous. The condition of the three lobes of the lung remained the same as at the previous operation. The pleura was incised vertically over the surface of the cyst. No cleavage plane could be found. In consequence, the cyst was freely opened and with a finger introduced into its cavity it was excised to its base by sharp dissection, including the overlying pleura which could not be detached. The medial wall was intimately adherent to the esophagus along the latter's central two-thirds and this long narrow base of the cyst could not be excised completely. However, the mucosal surface of the base was stripped off and two gauze packs placed against the remaining base and led out through either extremity of the thoracotomy wound. There was relatively little hemorrhage. The wound was then approximated closely about the packs.

The child's condition was precarious at the end of the operation. After intravenous glucose followed by transfusion his condition improved and he subsequently made a satisfactory convalescence. The gauze drains were removed on the tenth postoperative day following which the sinuses gradually granulated in without infection and the wound was entirely healed by the end of a month. This boy has been followed for sixteen years since his discharge from the hospital and has developed normally with only slight residual weakness of the right shoulder as a result of operative obliteration of the esophageal duplication. (See photograph and x-ray picture of chest, Fig. 1.)

*Pathologic Examination.*—Examination of the cyst wall showed it to have the histologic characteristics of stomach wall. There was a typical gastric mucosa containing chief and parietal cells with an underlying muscularis mucosa, submucosa, and muscularis. Rugae were present in some areas with strands of smooth muscle as seen in the normal stomach wall. The mucosa was destroyed in areas with fibrous tissue replacement and scattered throughout there were areas of hemorrhage and cellular infiltration.

*Diagnosis.*—Esophageal duplication lined by gastric mucosa.

CASE 2 (No. 118048).—J. B., a white, male infant, was admitted to the hospital Sept. 14, 1927, at the age of 7 weeks, because of feeding difficulties and failure to gain.

The family history was negative. The birth weight was 9¾ pounds. The neonatal period was uneventful except for paroxysms of pain when nursing. These were characterized by doubling up of the legs and screaming, with some regurgitation of feedings. A small amount of dark blood was vomited on one occasion. For several days he had been coughing frequently.

*Physical Examination.*—Examination revealed a pale, undernourished infant with rapid labored respirations. Temperature was 100.6° F. Further examination revealed head, eyes, ears, nose, and throat, negative; heart and lungs, not remarkable on admission except for slight dullness and a few scattered râles over the right apex posteriorly. Abdomen, nontender with no masses; rectal, reflexes, and extremities, negative.

Laboratory work showed a red blood count of 3,600,000, hemoglobin 60 per cent, white blood count 21,500 with 74 per cent polymorphonuclears. Wassermann was negative. Tuberculin was negative in dilution 1:25.

Röntgenograms of the chest showed a diffuse hazy infiltration of the entire right upper lobe.

The infant had a febrile course with increasing respiratory difficulty. Regurgitation of feedings persisted but barium studies showed no obstruction or displacement of the esophagus and no abnormality of the gastrointestinal tract. After several weeks he developed dullness over the whole right side of the chest with diminished breath sounds over the upper lobe. Repeat roentgenograms of the chest showed almost complete opacity of the right lung field with some mediastinal displacement to the left side. An area of pressure erosion was identified in the region of the angles of the fourth and fifth ribs posteriorly. Thoracentesis was carried out in this area and 10 c.c. of thick, viscid, mucoid fluid was aspirated under considerable pressure. This contained 700 cells per cu. mm., mostly red cells with a moderate number of lymphocytes. Smear and culture revealed no organisms. No hairs or epithelial cells were encountered. The following day a second tap was performed and after aspiration of 35 c.c. of the same type of fluid 10 c.c. of lipiodol were injected. Roentgenograms of the chest at this time showed a large cystic tumor of the posterior mediastinum extending toward the apex of the right lung and displacing both esophagus and trachea anteriorly.

Exploratory thoracotomy was carried out under gas-oxygen anesthesia, the mediastinum being entered extrapleurally through the beds of the resected posterior segments of the third and fourth ribs. Because of respiratory difficulties an adequate exploration could not be performed and the child was returned to his bed in a precarious condition. Four weeks later a second attempt was made and again the cyst could not be located, hurried exploration being necessary because of the child's poor condition. After an extremely stormy postoperative period characterized by recurrent bouts of bronchopneumonia the patient was discharged to a convalescent home.

At the age of 1 year the baby was readmitted in the hope that surgical approach to the cyst might be more successful. The general symptoms were unchanged. His weight at this time was 11 pounds. There was dullness and breath sounds were absent over the entire right upper chest with numerous râles over the right lower lobe and the entire left lung field. Fingers were definitely clubbed.

Several thoracenteses failed to enter the cyst. Recurrent exacerbations of chronic pneumonia prevented further surgical exploration. The patient finally succumbed to severe bronchopneumonia at the age of 16 months weighing at that time 10½ pounds.

*Autopsy.*—Autopsy revealed a 5 cm. cystic mass lying in the right paravertebral gutter adjacent to the esophagus and attached to the posterior chest wall and pleura over the right apex. The cyst was retropleural and had eroded the bodies of the upper thoracic vertebrae as well as the adjacent ribs. There was diffuse interstitial pneumonia, both acute and chronic.

Gross examination of the cyst showed it to resemble a portion of the gastrointestinal tract. There was a pleural reflexion resembling a serosa, a two-layered muscularis, a definite submucosa and a thick velvety mucosal lining which was thrown into numerous folds similar to gastric rugae. The cyst was not attached to the esophagus, trachea, or bronchi.

Microscopic examination revealed a typical gastric mucosa with deep branching glands lined by chief and parietal cells.

*Diagnosis.*—Esophageal duplication lined by gastric mucosa.

CASE 3 (No. 211576).—N. C., a 7-month-old girl, was admitted to the Children's Hospital, April 22, 1937, with a complaint of intermittent abdominal cramps of six months' duration.

Family history was irrelevant. Past history showed that the baby was delivered normally at full term, weighing  $7\frac{1}{2}$  pounds. The neonatal period was uneventful. She took feedings well and made a steady weight gain, reaching 13 pounds at six months. Since the first month of life the infant had been subject to occasional bouts of "abdominal cramps," which doubled her up and caused her to scream. In the six weeks prior to entry she had had these episodes four to five times per week and had developed anorexia with failure to gain. Ten days before admission she developed a dry cough, accompanied by fever and transitory cyanosis. Since that time she had refused to lie on her right side and had persistent respiratory distress, cough, and temperature ranging between 100 to 103° F. Vomiting of feedings occurred two to three times daily. Stools remained essentially normal without blood. There was no hematemesis or hemoptysis.

*Physical Examination.*—Examination on admission revealed a fairly well-developed, somewhat undernourished 7-month-old baby girl with slight cyanosis, breathing with difficulty. Examination of head, eyes, ears, nose, and throat was negative. The neck was short and the thoracic cage asymmetrical, there being a diffuse bulging of the right side of the chest posteriorly. The respiratory excursion was diminished on the right side. On percussion there was flatness over the right lung posteriorly with hyper-resonance anteriorly. Breath sounds were diminished on the right side posteriorly. There was questionable shift of the heart and mediastinum to the left. The heart was not enlarged, and there were regular rhythm, sounds of good quality, and no murmurs. The abdomen was soft and relaxed with no tenderness, spasm, or masses. The liver edge was palpable two fingers below the costal border. Examination of the genitals, rectum, reflexes, and extremities was essentially normal.

Laboratory work on admission showed a white blood count of 18,000 with 76 per cent polymorphonuclear leucocytes. Red blood count was 4,880,000 with 75 per cent hemoglobin. Urinalysis was negative. The blood Hinton test was negative.

Roentgenograms of the chest showed a large spherical mass about 8 cm. in diameter filling most of the right hemithorax and displacing the heart to the left. Fluoroscopy of the esophagus showed it to be displaced to the left in its lower third by the mass (Fig. 2).

*Course.*—A few days after admission, mediastinal exploration was carried out under cyclopropane anesthesia. A transpleural approach through a right posterolateral thoracotomy with resection of a segment of the seventh rib revealed an orange-sized cystic mass occupying the lower third of the right hemithorax. The cyst was retropleural in location and had a sessile attachment to the lower third of the esophagus. After freeing the periphery of the mass from the mediastinal pleura, marsupialization of the cyst was carried out by first aspirating its contents (about four ounces of brownish serous fluid) and then suturing the wall of the cyst to the wound edges with interrupted silk sutures. The chest was then closed in layers to the marsupialized cyst, following which a circular segment was excised from the exteriorized cyst wall and a rough gauze pack inserted into the cavity.

The postoperative course was uneventful. The marsupialized cyst drained copious amounts of watery fluid which had an acid reaction. Barium swallows showed no luminal connection between the esophagus and the cyst.

Fifteen days after marsupialization, excision of the cyst was undertaken under cyclopropane anesthesia. The marsupialized segment of the cyst was dissected free from the wound edges, the old thoracotomy wound opened, and dissection in the region of the attachment of the cyst showed the latter to be connected to the right side of the esophagus at the junction of its middle and lower thirds. No cleavage plane could be found and there seemed to be a common muscularis. Accordingly, the base of the cyst was cut across and the cyst removed

leaving a defect measuring about 3 by 2 cm. in size in the esophageal wall. The esophageal defect was closed by bringing the submucosa and muscularis together with a continuous suture of fine silk. The chest was closed with drainage of the pleural cavity.

The patient's postoperative course was stormy and on the third postoperative day the esophageal suture line broke down with the establishment of an esophagopleural fistula. Consequently, two days later, the chest was reopened in an attempt to close the fistula. The child did poorly during the operation, however, and a hurried closure of the esophageal defect was carried out with interrupted fine chromic catgut mattress sutures to submucosa and muscularis in two



Fig. 2 (Case 3, N. C.).—Note large esophageal duplication filling two-thirds of right hemithorax.

rows. Again, the chest was closed with drainage. About one week postoperatively saliva and curds appeared on the dressings despite the fact that the child had been maintained on gastric feedings via a Levin tube. The re-established esophagopleural fistula soon began to drain copious amounts of saliva, amounting to eight to ten ounces daily.

A gastrostomy was performed, but despite carefully regulated feedings the child's nutrition was maintained with difficulty because of frequent episodes of diarrhea, vomiting, and recurrent bouts of pneumonia.

About one year after the last attempted closure of the esophageal defect, the chest sinus completely closed over, but fluoroscopic study of the esophagus with barium revealed the persistence of a fistulous tract connecting the esophageal lumen and a cystic mediastinal cavity. Consequently, a second attempt at closure of the esophageal fistula was carried out by the transpleural route. Because of multiple adhesions, dissection was difficult. A lemon-sized sac was encountered in the right side of the posterior mediastinum. This was dissected free with considerable difficulty and was found to be attached to the esophagus by a narrow 3 cm. fistulous tract measuring about one inch in diameter. This tract was freed, clamped, and divided close to the esophagus, leaving a defect in the wall of the latter about one inch in diameter. The defect was closed by approximating mucosa with interrupted fine silk, muscularis with mattress sutures of the same material, and finally bringing adjacent pleura over the suture line with a continuous suture. At this point in the procedure the child's respirations became shallow and irregular, and complete excision of the sac could not be performed—instead, it was partially excised and the remainder marsupialized into the thoracotomy wound, packed with rough gauze, and the chest wall closed.

Four days after this procedure the esophageal suture line broke down and the fistula was re-established. Copious amounts of saliva were drained from the child's chest wound. Two months after this last attempted closure she developed a severe diarrhea associated with interstitial pneumonia and died at the age of 1 year, 11 months, thus ending a fifteen months' hospital stay.

*Pathologic Findings.*—The surgically excised cyst measured 5 by 6 cm. Its external surface was covered by a serous capsule (pleura) through which the muscular wall appeared pale gray in color. There were two distinct muscular lamellae, each about 2 mm. thick, and on the inner surface a smooth, mucosal lining, yellowish red in color with large rugae and measuring from 1 to 2 mm. in thickness. Microscopic examination revealed the mucosa to be of gastric type. There were large branching glands of mucus-secreting cells with smaller deeper cords of glands lined by parietal and chief cells. The submucosa was a well-defined structure without inflammatory infiltration. Two layers of smooth muscle constituted the muscularis.

*Diagnosis.*—Duplication of esophagus lined by gastric mucosa.

*Autopsy.*—Examination revealed a fistulous tract extending from the lower third of the esophagus through the right posterior pleural cavity to the chest wall. There were extensive fibrous pleural adhesions adjacent to the fistula, but there was no empyema. The right lower lobe of lung contained large areas of fibrosis. In addition there were multiple areas of lobular atelectasis and diffuse interstitial pneumonia, both acute and chronic, involving all lobes of both lungs. Aside from signs of malnutrition, there were no other significant findings.

CASE 4 (No. 257878).—P. H., a 3-week-old boy, was admitted to the Surgical Service of The Children's Hospital because of a mediastinal mass discovered roentgenologically in a film of the spine taken in the routine orthopedic work-up of clubfeet. Birth was at full term, with normal delivery, and uneventful neonatal period. The baby weighed 9 pounds at birth, took breast feedings well, and gained to 10 pounds at the time of admission. Bilateral talipes equinovarus noted at birth had brought the infant to the orthopedic outpatient department. The mediastinal mass discovered by roentgenogram had apparently caused no symptoms whatever. There was no respiratory distress, cough, cyanosis, hemoptysis, feeding difficulty, pain, or vomiting.

*Physical Examination.*—Examination on admission showed a well-developed and well-nourished male infant, in no distress. Color and hydration were good. Examination of head, eyes, ears, nose, and throat was negative. The trachea deviated about 1 cm. to the right of the midline at the suprasternal notch. The heart was

not enlarged, but the border on the right side of the heart was percussed about 2 cm. to the right of the sternum. The apical impulse was palpable at the left sternal border in the fourth interspace. Heart sounds were of good quality and there were no murmurs. The lungs were clear to auscultation and percussion. No areas of dullness could be made out. There were no râles. The abdomen was soft and non-tender with no palpable organs or masses. Genitals, rectum, and reflexes were found to be normal on examination. There was bilateral talipes equinovarus, more marked on the left side.

Laboratory work on admission showed negative urinalysis, red blood count 4,940,000, hemoglobin 80 per cent, white blood count 9,700 with a normal smear. Blood Hinton test was negative.

Roentgenograms of the chest showed the heart and mediastinum to be displaced to the right by a large, 5 cm., rounded, well-circumscribed soft tissue mass in the posterior mediastinum, situated behind the heart and extending out into the left hemithorax. Fluoroscopic examination of the esophagus with barium showed that the esophagus was displaced forward and to the right by the mass.

*Course.*—Shortly after admission mediastinal exploration was carried out under cyclopropane anesthesia. The chest was entered through a left posterolateral thoracotomy, resecting the posterior segments of the eighth and ninth ribs subperiosteally. Upon opening the pleura a soft, yellowish-gray, cystic mass was noted in the lower third of the thorax. This was retropleural in location, measured about 5 cm. in diameter, and was roughly spherical. Dissection readily freed the periphery of the cyst from the overlying pleura and it was found to be attached by a pedicle about 1.5 cm. wide to the left wall of the esophagus at the junction of the latter's middle and lower thirds. The cyst was then grasped with Allis forceps, drawn into the thoracotomy wound, and sutured to the pleura and intercostal muscle with interrupted 6-0 silk. The chest wall was then closed in layers with silk to the marsupialized cyst, following which the exteriorized cyst wall was incised with the escape of three to four ounces of watery, blood-tinged fluid. Biopsy was done on a segment of the wall and the margins of the marsupialized cyst were sutured to skin edges with interrupted 6-0 silk sutures. The cyst's cavity was then packed firmly with gauze.

The baby's postoperative course was satisfactory. The exteriorized cyst drained moderate amounts of clear fluid which had an acid reaction. The gauze packing was changed frequently at first. Feedings were taken well by mouth, and there was no evidence of a connection between the esophageal lumen and that of the cyst by clinical observation or by lipiodol injection.

About one month after the original operation, the lining membrane of the marsupialized cyst was curetted thoroughly, snugly packed with gauze, and the pack left in place for one week. Following this procedure the discharge from the sinus steadily decreased. The child was discharged home two months after entry and follow-up was carried on in the outpatient department. The sinus continued to discharge small amounts of serous fluid, necessitating daily dressings. The baby's general condition remained excellent and he gained well.

Nine months after the original operation the baby was readmitted because of persistence of discharge from the chest sinus and curettage was again carried out. At this time pathologic study of the curettings failed to show any mucosa but only granulation tissue and fibrinopurulent exudate. After a curettage of the lining membrane a gauze pack was again inserted. Postoperatively the discharge diminished temporarily, but soon became fairly profuse again. Consequently, one month later a secondary marsupialization of the cyst was performed under cyclopropane anesthesia. The cyst wall was dissected free down to the esophagus, mobilizing the former adequately to allow excision of a cuff of distal cyst wall about 3 cm. long. The cavity was again thoroughly curetted, treated with 95 per

cent alcohol, and repacked with gauze. Postoperatively, the baby did well, and the sinus gradually filled in with granulation tissue, being solidly healed in a month.

Follow-up has been continued for three and one-half years and there has been no subsequent evidence of recurrence of the cyst by clinical or roentgenographic observations. The patient has developed normally and has no symptoms relative to his esophageal duplication (Fig. 3).

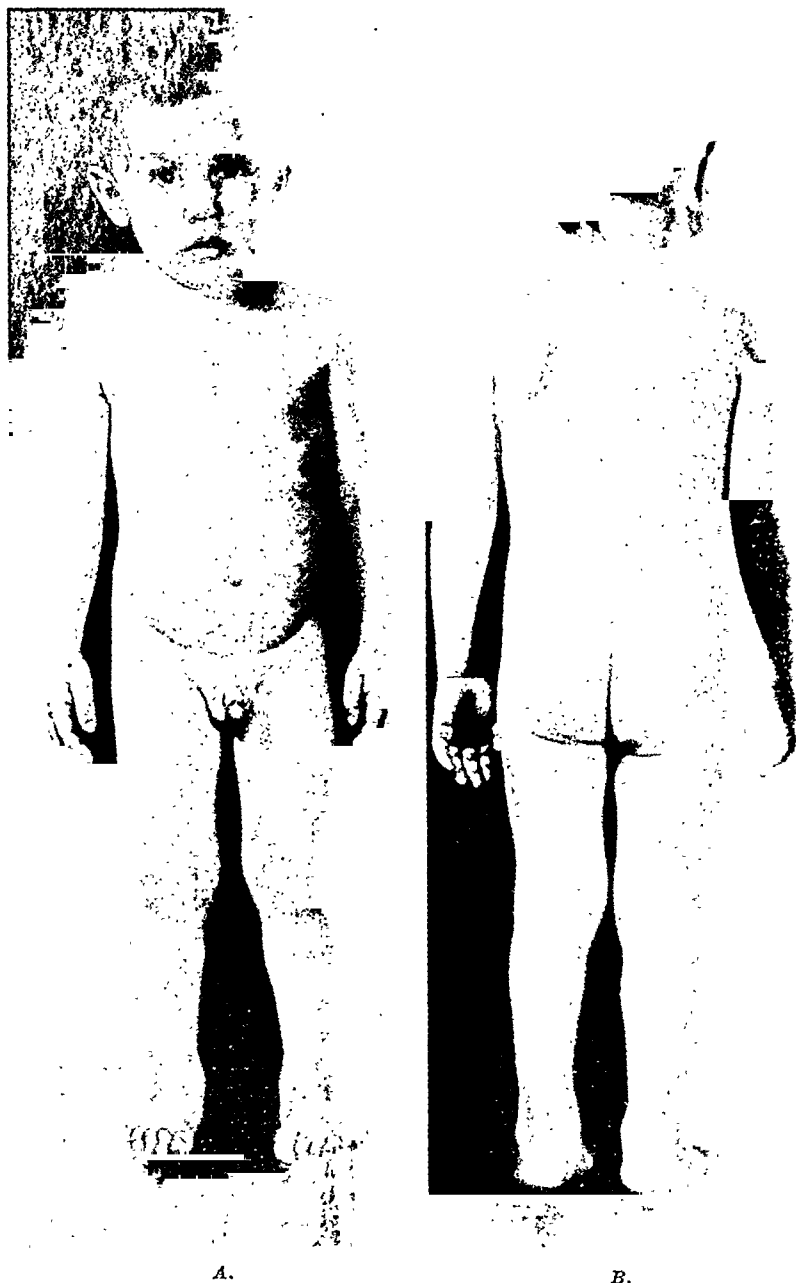


Fig. 3 (Case 4, P. H.).—Aged 2-10/12 years. Two and one-half years following treatment of esophageal duplication.

*Pathologic Findings.*—The segment of the wall of the cyst showed it to be about 4 mm. thick. The pleura was reflected over and adherent to the outer surface resembling a serosa. The inner surface was lined by a pale, yellowish mucosa with definite rugae. Microscopic sections of the wall of the sac showed it to consist of a double layer of smooth muscle, a submucosa, muscularis mucosae, and a well-developed mucosa. The mucosa was characterized by fairly deep branching glands, lined by mucous cells near the surface, whereas the lower portions of the glands contained chief and parietal cells. The entire picture was characteristic of gastric mucosa. No abnormalities of the structure of the wall or of the mucosa were noted.

*Diagnosis.*—Duplication of esophagus lined by gastric mucosa.

CASE 5 (No. 273768).—E. B., a 2-year-old boy, was first admitted to the Infants' Hospital at the age of 1 year because of hemoptysis of three days' duration. Family history was noncontributory. Past history showed that the child was delivered normally at full term, weighing 7 pounds, with an uneventful neonatal period. The baby had been well until one week before admission when he developed an upper respiratory infection with coryza, cough, and low-grade fever. In the three days prior to admission the patient coughed or "spit up" bright and dark blood in small amounts on several occasions.

*Physical Examination.*—Examination on admission showed a poorly nourished, underdeveloped, pale boy with slightly labored respirations. Temperature was 99.6° F.; pulse, 172; respirations, 32; weight, 15 pounds. Examination of head, eyes, ears, nose, and throat was negative. The chest was symmetrical and the lungs were resonant throughout. Breath sounds were vesicular with a few scattered, coarse râles over the right base posteriorly. Heart was within normal limits. Abdomen, genitals, rectal, extremities, and reflexes were not remarkable.

Laboratory work on admission showed negative urinalysis, red blood count 3,350,000, with hemoglobin 40 per cent. White blood count was 39,900 with 61 per cent polymorphonuclears and marked hypochromia of red cells on smear. Tuberculin was negative in dilution 1:100. Stool showed +++ guaiac test. Bleeding, clotting, and prothrombin times were within the normal range.

*Course.*—Roentgenogram and fluoroscopic examination of the chest showed rather dense infiltration of the medial third of the right lung, more marked in the right lower lobe. In addition, there was a rounded, circumscribed, soft tissue mass about the size of an orange lying in the central portion of the posterior mediastinum on the right. This caused no cardiac displacement (Fig. 4). Bronchoscopy with lipiodol bronchograms was next carried out showing no bleeding point or ulceration in the tracheobronchial tree. There was some downward displacement of the right lower lobe bronchus by the posterior mediastinal mass but bronchograms were otherwise negative. Barium fluoroscopy of the esophagus showed no distortion or encroachment upon the latter by the mediastinal mass. An esophagoscopy showed no varices, ulcerations, or any other source of bleeding. Gastrointestinal series was negative.

During this period of studies the baby had a low-grade fever, cough, and several episodes of coughing or "spitting up" blood. It could never be conclusively decided as to whether he had hemoptysis or hematemesis. He was maintained on sulfadiazine and given several small transfusions.

Mediastinal exploration was decided upon after consultation between medical, surgical, and roentgenologic services. Diagnoses which were entertained included mediastinal tumor, mediastinal effusion or empyema, and esophageal duplication. Consequently, on the eighteenth hospital day mediastinal exploration was carried out through a right posterior thoracotomy under cyclopropane anesthesia. Posterior segments of the fourth and fifth ribs were resected subperiosteally. The



A.



B.

Fig. 4 (Case 5, L B) —Chest roentgenograms before first operation (A) and two months after second operation (B)

pleura was stripped down off the rib necks and the vertebral bodies in an extrapleural approach to the mediastinal mass. This was only partially successful, however, as the pleura was inadvertently opened and the underlying lung appeared to be rubbery hard in consistency and densely adherent to a poorly circumscribed extrapleural mass which filled the right paravertebral gutter. The pleural defect was then closed and extrapleural dissection into the mediastinum revealed an extremely vascular mass of adherent inflammatory tissue which contained old clotted blood in its midst. No cleavage planes could be found around this mass. The esophagus could not be identified. No cyst, discrete tumor, or fluid collection was encountered. As the center of the mass was broken into there was a very brisk hemorrhage which could be checked only by tight packing. The child's condition at this point became critical despite transfusion, and further investigation of the mass was out of the question. Consequently, the wound was rapidly closed in layers around the pack which was left in place and led out through the lower angle of the incision.

The immediate postoperative period was extremely stormy. Bleeding from the mediastinal mass continued at an alarming rate necessitating frequent changes of pack and multiple transfusions. The baby developed considerable pneumonitis with pleural effusion and also a *Staphylococcus aureus* wound infection, undoubtedly related to the repeated packings which were necessary to control the persistent bleeding from the mediastinal lesion. Sulfadiazine was administered in full doses. Three weeks after the first operation a second procedure was carried out under local anesthesia in an effort to obtain a biopsy of the mediastinal mass and to stop the persistent hemorrhage. Again, the child's precarious condition prevented anything more than biopsy and tight packing of the profusely bleeding sinus leading into the posterior mediastinum.

The biopsy showed only granulation tissue and no satisfactory diagnosis could be made. Repeated chest pictures offered no clue as to the nature of the lesion. On the basis that we might have been dealing with hemangioma or a malignant neoplasm which had possibly eroded the wall of one of the great vessels, a course of roentgen therapy was given (a total of 2,100 r. over the chest and back).

Two months after the first operation the bleeding tendency stopped and the wound could finally be left open without packing. It slowly granulated in and was solidly healed in another month. During this period the child's nutrition and general health improved markedly. X-ray pictures of the chest showed the posterior mediastinal mass to be smaller but still present. There were no subsequent episodes of hematemesis or hemoptysis.

The child was sent to the convalescent home for several weeks and continued to improve in nutrition. However, a follow-up chest roentgenogram at this time showed a definite destructive lesion of the bodies of the sixth and seventh thoracic vertebrae consistent with osteomyelitis. Consequently, he was readmitted to the hospital at the age of 17 months. Examination at this time showed slight dorsal kyphosis. There was a tiny sinus at the bottom of the old depressed thoracotomy scar which drained small amounts of seropurulent material culturing *Staphylococcus aureus*. The baby was immobilized in hyperextension on a Bradford frame for two months and then placed in a plaster shell. The sinus healed completely and roentgenograms showed healing of the osteomyelitis. One episode of hemoptysis occurred when he was 19 months of age. Chest roentgenograms at the time showed the mediastinal mass to be even smaller, and gastrointestinal series was negative.

Once more the child was sent to the convalescent home in his plaster shell and remained essentially asymptomatic for two and one-half months when small amounts of dark blood were noted to be draining from the small thoracotomy sinus which had re-opened.

He was re-admitted to the hospital and examination of the chest wound was essentially as before excepting that the edges of the tiny sinus appeared to be macerated. Black, changed blood was draining from the opening in small quantities. A few days after admission a few drops of clear fluid appeared in the sinus opening (Fig. 5). This had a pH of 4.0. Repeated specimens were collected for chemical analysis showing acidity ranging constantly between pH 3.5 and 4.5, definite peptic and rennin activity. Chloride was 120 meq./l with sodium 89 meq./l. Roentgenograms with lipiodol instillation into the sinus by means of a ureteral catheter showed a narrow tract about 3 to 4 cm. long extending to a cystic cavity about the size of a walnut in the right paravertebral gutter opposite the sixth dorsal vertebra. Barium fluoroscopy of the esophagus at the same time showed no displacement or abnormality of the latter's contour, although the cyst lay close beside it.



Fig. 5 (Case 5, E. B.).—Photograph of back ten months after first operation showing sinus discharging "gastric juice."

Finally a definite diagnosis became apparent: esophageal duplication lined by gastric mucous membrane. The child was operated on again (approximately one year after his original hospital entry); under cyclopropane anesthesia the sinus tract was first dilated and curetted and then dissected out down to the extra-pleural cystic cavity. Upon excising the sinus tract the fundus of the little cyst could be visualized directly. It was thoroughly curetted in an effort to remove all mucosa down to the gristly muscular wall. The wall was then treated with tincture of iodine and the cavity tightly packed with about seven feet of three-quarter inch iodoform gauze. This was left in place for ten days and then re-

moved and the cavity allowed to granulate in. Healing was complete in four weeks with no further discharge to suggest residual mucosal lining. At the time of this report, the osteomyelitis of the vertebrae remains quiescent and seems satisfactorily healed. The child is still under observation but will be discharged home shortly.

*Pathologic Report.*—Examination of the cyst wall and curettings showed a mucous membrane which was histologically identical with gastric mucosa and entirely consistent with esophageal duplication lined by a gastric type of mucosa (Fig. 6).



Fig. 6 (Case 5, E. B.).—Photomicrograph of lining of esophageal duplication in Case 5. Note typical gastric mucosa.

#### PATHOLOGY

Esophageal duplications are cystic structures of variable size possessing thick walls and a mucous membrane lining. They arise in the posterior mediastinum and usually expand into the right or left hemithorax, remaining retropleural in location. The cysts have been encountered along the entire length of the mediastinum but are most common in the middle third.

Histologically, the duplications usually have a two-layered muscular wall resembling esophagus. The mucosa, however, does not necessarily correspond to that of esophagus, but may closely simulate gastric mucosa. Some of the cysts have elements of both esophageal and gastric mucous membranes. A true serosa is absent, although the pleura is occasionally reflected over the larger cysts so as to resemble grossly a serosal coat.

Perhaps the most significant fact from a surgical viewpoint regarding their histology is the frequency of an intimate attachment to the esophagus. The muscular coats are usually densely adherent to those

of the esophagus and, indeed, there may be a common muscularis between the two structures. A few of the duplications have been found to have no attachment whatsoever to the esophagus.

One of our cases falls into the latter group, while in three patients the duplications were attached to the esophageal wall with no intervening plane of cleavage. In one individual the cyst's attachment could not be determined at operation. None of the duplications in our series had a fistulous communication with the esophageal lumen as occasionally found in duplications of the intestine. Such a connection is a theoretical possibility but has never been reported, to our knowledge.

The contents of the cysts usually resemble gastric juice. In our last patient the fluid gave positive tests for rennin and pepsin. As the acid-secreting elements of gastric mucosa are frequently present, high titers of hydrochloric acid may be encountered. One case is reported in the literature<sup>4</sup> of peptic ulcer developing in an esophageal duplication and giving rise to a fatal issue by perforating into the pleural cavity and lung. Peptic ulceration best explains the changes found at the first operation in Case 5 in our series.

The cysts vary considerably in size. Our largest specimen filled two-thirds of the right thoracic cavity in a 22-month-old boy. The others averaged about 5 cm. in diameter. Four of our patients had a typical gastric type of mucosa, while the other presented a lining membrane resembling esophageal mucosa in some areas, gastric in others, and duodenal in still other sections.

#### EMBRYOLOGY

Numerous theories have been proposed in an attempt to explain the occurrence of alimentary duplications in general.<sup>1, 2, 4, 5</sup> Those occurring along the course of the small bowel were formerly thought to be related in some fashion to Meckel's diverticulum. Twinning affecting only a portion of the alimentary tube has been advanced as a possible explanation, but proof of such occurrence is lacking.

Lewis and Thyng<sup>6</sup> found diverticula frequently in the fetal alimentary tract of pigs, rabbits, cats, sheep, and man. According to these authors, such diverticula normally regress, but persistence or sequestration of a "knoblike outpocketing of intestinal epithelium" might give rise to an adjacent duplication either separate from or connected with the alimentary wall or lumen. However, diverticula resembling those described in fetuses by Lewis and Thyng are extremely rare in early postnatal life. The clinical evidence also fails to suggest their theory. The fetal diverticula were most common in the region of the duodenum while alimentary duplications are found most frequently in the lower jejunum and ileum. Nevertheless, it is possible that some duplications have their origins in such diverticula.

According to Keith<sup>7</sup> the development of an alimentary duplication is analogous to that of an atresia. In the latter there is a failure of coalescence of vacuoles in the solid stage of the alimentary tube in its longitudinal axis so that the continuity of the lumen is not established aborally. Keith feels that a duplication results from failure of coalescence of such vacuoles in a transverse manner. Thus, a cystic structure is left contiguous to some portion of the alimentary tract. Bremer<sup>8</sup> supports this theory and points out that the various forms of a duplication's attachment can be explained by the relative distance of the sequestered vacuoles from the true lumen of the primitive alimentary tube. That is to say, if the sequestered vacuoles are close to the lumen, the duplication which develops may be separated from the alimentary lumen only by two layers of mucosa, which may undergo necrosis, thus giving a luminal connection between gut and duplication or, if the distance be greater, submucosal and muscular layers may intervene, until with the greatest degree of separation there may be no attachment at all between the duplication and the alimentary tube.

The ideas of Keith and Bremer offer the most rational explanation of the embryologic development and subsequent form of alimentary duplications as encountered by the surgeon.

#### CLINICAL ASPECTS

Duplications of the esophagus, like the other forms of alimentary duplication, are usually encountered in infancy and early childhood. Our youngest patient was 3 weeks of age, while the oldest was 22 months. The oldest recorded case in the literature was a boy  $3\frac{1}{2}$  years of age.<sup>9</sup> Both sexes are equally involved regarding incidence.

The symptoms caused by esophageal duplication are not only those of an expanding mediastinal mass, but in addition there may be the complicating features of peptic ulceration of the wall of the cyst.

Cough, dyspnea, cyanosis, and recurrent or chronic pneumonias are common presenting complaints referable to pulmonary compression and extrinsic bronchial obstruction by the encroachment of the duplication.

Dysphagia and regurgitation of feedings occur with impingement upon the esophageal lumen.

Apparently pain may be caused by distention of the walls of the duplication with increased intracystic pressure.

Hematemesis and hemoptysis may occur separately or even in the same patient. The former probably results from damage to the blood supply of the esophageal wall by the expansion of the adjacent cyst with resultant sloughing of the esophageal mucosa. Hemoptysis occurred in one individual reported in the German literature<sup>4</sup> as a result of peptic ulcer in an esophageal duplication penetrating into the overlying lung. Three of our patients had repeated hemoptyses as a result of pulmonary compression with superimposed pneumonia.

Physical examination usually discloses definite indications of thoracic disease, but rarely allows the clinician to make a specific diagnosis. Obvious respiratory difficulty and cyanosis are common. Malnutrition and the hallmarks of chronic illness are frequently present. There may be a massive pleural effusion. Signs of chronic pneumonitis and pulmonary compression may be found. Occasionally the duplications are large enough to cause shift of the heart and mediastinum.

Our youngest patient (P. H.), aged 3 weeks, had no apparent symptoms and practically no physical signs of esophageal duplication, the presence of the cyst being disclosed inadvertently by a roentgenogram of the spine taken in the routine orthopedic work-up for club feet.

#### ROENTGENOLOGIC FINDINGS

Esophageal duplications present roentgen changes characteristic of posterior mediastinal tumors or cysts. Details of the duplication's outline may be obscured by secondary changes in the lung and particularly by pleural fluid. Most duplications are roughly spherical in contour and have a uniform homogeneous density due to their fluid content. The heart and mediastinal structures may be displaced.

Lipiodol bronchograms usually show pulmonary compression by the retropleural duplication, and aid in differentiating the latter from bronchogenic cysts and anomalies. Fluoroscopy of the esophagus with contrast media showed no fistulous connection between duplication and esophagus in any of our patients. However, the esophagus was frequently displaced or angulated by the adjacent mass.

Esophageal duplications occasionally erode the bodies of the thoracic vertebrae or the overlying ribs.

#### TREATMENT

The most significant fact to be considered in the surgical extirpation of esophageal duplications is that, with rare exception, they share a common muscularis with the esophagus itself. Thus, there is obviously no plane of cleavage to be found between the duplication and the esophagus, and an attempted excision may result in an extensive defect in the esophageal wall. The cyst's attachment is frequently widely sessile. In one of our cases (D. S.) the attachment consisted of about two-thirds of the length of the esophagus.

Because of the nature of the attachment of esophageal duplications, extirpation of the cyst by means of marsupialization with subsequent destruction of the mucosal lining appears to us to be the most conservative and by far the safest procedure. Experience with our own cases seems to bear this out.

In every case we have approached the duplication through a posterior or posterolateral thoracotomy entering the pleural cavity on the side in which the greater portion of the cyst presented. The duplication can usually be readily dissected free from the adjacent lung.

In three instances the duplication was then marsupialized by freeing it thoroughly except from its esophageal attachment and then drawing the most readily available portion into the thoracotomy wound. The pleura was then sutured circumferentially to the wall of the duplication and the chest wall closed in layers, the lung being re-expanded by catheter-suction technique. After the closure of the wound the marsupialized segment of cyst was opened, contents aspirated, and the cavity packed with rough gauze to destroy the mucosal lining (Fig. 7).

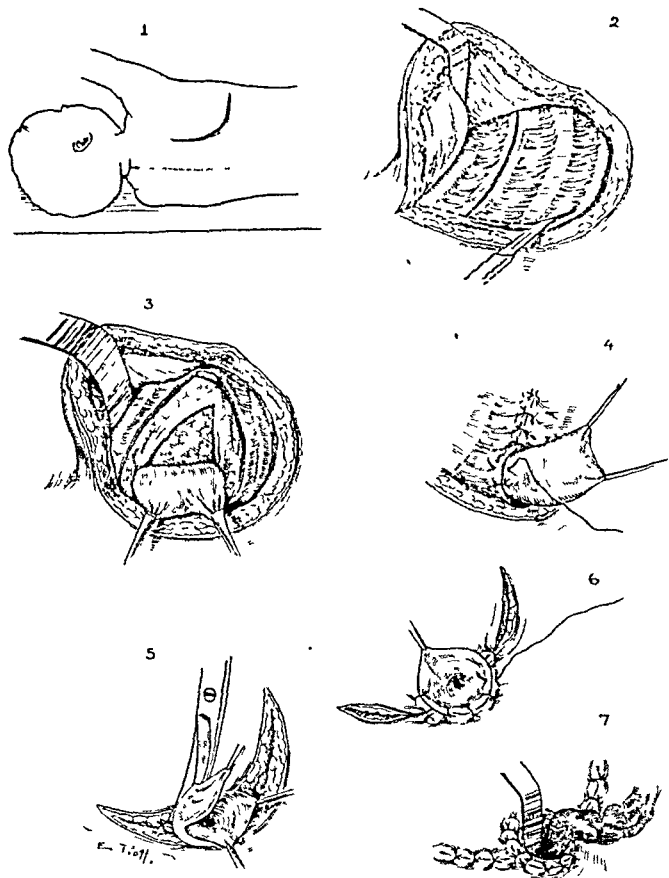


Fig. 7.—Operative drawings showing stages in operative technique of marsupialization of duplication of esophagus

By adopting this technique the dangerous complications of esophago-pleural fistula and mediastinitis are obviated. The mucosal lining of the cyst can be destroyed by packing or by the use of sclerosing solutions, allowing the denuded walls of the cyst to fall together with subsequent spontaneous obliteration of the duplication.

In two individuals an attempt was made to excise completely the marsupialized duplication as a second stage procedure. In one of



these, partial excision of the cyst was done, leaving the medial wall attached to the esophagus and packing this and the pleural cavity with rough gauze. A chronic draining sinus developed, but the esophagus was not damaged and the patient recovered, the sinus closing completely in several weeks. In the other patient, excision of the duplication left a sizable defect in the esophageal wall. Although this was sutured in a seemingly satisfactory manner, a leak developed and an esophagopleural fistula was established. This persisted despite two subsequent attempts at closure and the patient finally succumbed to mediastinal, pleural, and pulmonary infection.

Our fourth patient was treated in a more satisfactory and safer manner by continually packing and curetting the cavity of the marsupialized cyst until the mucosa was destroyed and spontaneous closure of the sinus took place.

In our most recent case (E. B., Case 5) we were unable to make a conclusive diagnosis until almost twelve months after the child's initial hospital entry. The vascular inflammatory tissue which bled so profusely when the mediastinum was entered at the first operation apparently represented the bed of a penetrating peptic ulcer of an esophageal duplication, and because of the profuse hemorrhage and extensive inflammatory reaction the nature of the underlying lesion did not become clear until months later when the persistent wound sinus began discharging "gastric juice." Since we had unwittingly performed a marsupialization, although hardly in a manner to be recommended, it remained a simple matter to excise the sinus, widely exenterating the cystic cavity, and begin destruction of its mucosa by curettage and packing.

The first patient in this group of five cases had a small duplication which could not be found at exploratory thoracotomy, and subsequently he died with pneumonia. At post-mortem examination the duplication was found to be completely free from attachment to the esophagus, and represented one of the extremely rare types which might have been safely excised.

Thus, two of our five patients have died, while the other three have recovered. Follow-up on one of these (D. S.) has continued for sixteen years, another (P. H.) for two and one-half years, and the third (E. B.) is now in good health with the wound healed two months after his last operation. The first two children have developed normally and neither has any demonstrable disturbance of mediastinal or pulmonary anatomy or physiology at the time of this communication. The esophageal duplication has apparently been obliterated in the last individual, but full activity will not be allowed for several months because of the old osteomyelitis.

#### SUMMARY

1. Duplications of the esophagus are mediastinal cysts of developmental origin occurring along the course of the esophagus.

2. They possess muscular walls and mucous membrane linings which usually simulate gastric mucosa and are subject to peptic ulceration.

3. The cysts frequently have a common wall with the esophagus, thus rendering their complete excision almost impossible without esophageal damage.

4. Five individuals with esophageal duplications have been treated at The Children's Hospital during the last fifteen years. Case histories of these patients are reported in detail.

5. Experience with these individuals indicates that surgical extirpation of a duplication of the esophagus may best be accomplished by marsupialization of the cyst and subsequent destruction of its mucosal lining.

6. Three of our five patients have recovered.

#### REFERENCES

1. Ladd, W. E.: Duplications of the Alimentary Tract, *South. M. J.* 30: 363, 1937.
2. Ladd, W. E., and Gross, R. E.: Surgical Treatment of Duplications of the Alimentary Tract, *Surg., Gynec. & Obst.* 70: 295, 1940.
3. Mixer, C. G., and Clifford, S. H.: Congenital Mediastinal Cysts of Gastro-genic and Bronchogenic Origin, *Ann. Surg.* 90: 714, 1929.
4. Seydl, Gunther N.: Ein Kongenitale Magenwandcyste in Mediastinalraum mit in die Lunge perforierten Ulcus Pepticum. *Frankfurt. Ztschr. f. Path.* 52: 346, 1938.
5. Poncher, H. G., and Milles, G.: Cysts and Diverticula of Intestinal Origin, *Am. J. Dis. Child.* 45: 1064, 1933.
6. Lewis, F. T., and Thyng, F. W.: The Regular Occurrence of Intestinal Diverticula in the Embryos of the Pig, Rabbit and Man, *Am. J. Anat.* 7: 505, 1907.
7. Keith, Sir Arthur: *Human Embryology and Morphology*, Baltimore, Md., 1933, William Wood & Company.
8. Bremer, J. L.: Personal communication.
9. von Wyss, H.: Zur Kenntnis des heterologen Flimmercysten, *Virchows Arch. f. path. Anat.* 51: 143, 1870.

## PRIMARY LYMPHOSARCOMA OF THE BREAST

FRANK E. ADAIR, M.D., AND JULIAN B. HERRMANN, M.D.  
NEW YORK, N. Y.

*(From the Breast Department of the Memorial Hospital for Cancer and Allied Diseases)*

SINCE lymphosarcoma is a disease of the lymphatic structures, any part of the body containing lymphoid tissue may become involved. Enlargement of the superficial, retroperitoneal, or mediastinal lymph nodes is usually the earliest manifestation of the disease process. Later the malady may involve other organs and structures. In some instances the disease process may have its inception in an organ.

An organ infrequently affected by this disease, judging by the paucity of reported cases, is the breast. Gross, in 1880, removed a growth of three months' duration from the upper, outer border of the left mamma of a 22-year-old woman. The histologic diagnosis was lymphadenoid sarcoma. In 1913 Baumgartner wrote, "We know of only two cases of lymphosarcoma of the mamma. The first is that of Billroth and the second is that of Halsam." Geist and Wilensky, in 1915, reviewed the literature on sarcoma of the breast and compiled a list of 435 cases, of which 5 were classified as lymphosarcoma.

The number of authentic examples of breast involvement reported in the literature is further decreased if those are eliminated which are erroneously diagnosed as lymphosarcoma. As an illustration there is the case reported by McWilliams as bilateral lymphosarcoma of the breast in which the biopsy was "benign lymphoma" and the blood picture revealed a leucemia. It may reasonably be assumed that the breast lesions were leucemic rather than lymphosarcomatous manifestations. Also the differentiation between lymphosarcoma and round-cell sarcoma is not always clear. Thus Geist and Wilensky, in their previously mentioned review of breast sarcoma, said, "In two of our cases a previous diagnosis of lymphosarcoma of the breast had been made. The gross and histologic pictures of these tumors correspond accurately with those of round-cell sarcoma." On the other hand, Duany considered as primary lymphosarcoma the case which Heineke reported as round-cell sarcoma of the breast. In Elsberg's case of multiple lymphosarcoma of the breasts, the terms lymphosarcoma and round-cell sarcoma appear to be used interchangeably.

The confusion arises because of the inadequate classification of breast sarcomas. This is emphasized by Ewing, who says, "When one excludes from the group of mammary sarcomas the adenosarcomas, the malignant forms of mixed tumors containing cartilage, bone, mucoid, or fat tissue, and certain malignant round-, spindle-, and giant-cell

alveolar pseudosarcomas, which are really atypical carcinomas, there is little remaining of a once formidable group of mammary neoplasms. There are reasons for believing that such a disintegration of the group is justifiable. In fact, the situation today is much as it was in 1894, when Williams found it impossible to write the history of pure mammary sarcoma because of the absence of requisite data.

The round-cell sarcomas of various authors form an ill-defined group. They probably include very atypical tumors of the same nature as unclassified spindle-cell sarcomas, atypical carcinomas, and some pigment-free melanomas."

Lymphosarcoma of the breast may be a local manifestation of the disease which has originated elsewhere in the body, or it may be a primary lesion in this organ. The secondary focus may be a discrete metastatic lesion or it may be a direct extension from a mediastinal tumor. An example of the latter mode of involvement of the breast is the case described by Schoen. The patient had suffered from gynecomastia in his youth. This subsided, but at the age of 38 years both breasts underwent painless enlargement with no other evidence of disease. Eight months later nodules appeared in the skin of the scalp and trunk, followed by cervical and axillary lymphadenopathy. The patient died six months later and an autopsy revealed generalized lymphosarcomatosis with a huge mediastinal tumor and massive involvement of both breasts. There was a direct connection between the mediastinal tumor and the tumor in the left breast through the intercostal muscles. The tumor in the right breast was unconnected with the mediastinal mass.

Various writers on the subject of lymphosarcoma of the breast have been at a loss to explain the occurrence of the disease in this organ. Geist wrote, "We were unable to demonstrate that lymphoid tissue occurred normally either in the breast proper or in the skin overlying it, nor could we find references in the literature to its occurrence, and we were forced to conclude that lymphosarcoma does not occur primarily in the breast and that the tumors so classified heretofore were in all probability small, round-cell sarcomata." In his paper on lymphosarcoma of the breast Harrington says, "The explanation for the presence of a primary lymphosarcoma of the breast is rather difficult, since lymph follicles are not ordinarily located there, but the following suggestions may be made. Large collections of lymphocytes are found in the mammary gland in most chronic pathologic entities affecting the breast. Secondary lymph follicles may be formed and a continuation of the stimulus, whatever it is, may produce a malignant change."

On this phase of the subject Stewart and Foote\* were kind enough to contribute the following explanation: "There are commonly found

\*Dr. Fred Stewart and Dr. Frank Foote of the Department of Pathology, Memorial Hospital.

in the breast lymphoid infiltrates in the lobules and about the ducts. These, sometimes, are highly developed and contain definite germinal centers. There is every reason to believe that these are the origin of the lymphomas. Moreover, in some of the cases of lymphosarcoma seen at this hospital there are found foci of lymphomatous infiltrates of benign appearance and not in direct continuity with the true lymphosarcoma."

There are some intra- and juxta-node groups which may possibly be the site of origin of the disease in some instances. Their location may be indicated most clearly by the following brief description of the breast lymphatics (Fig. 1).

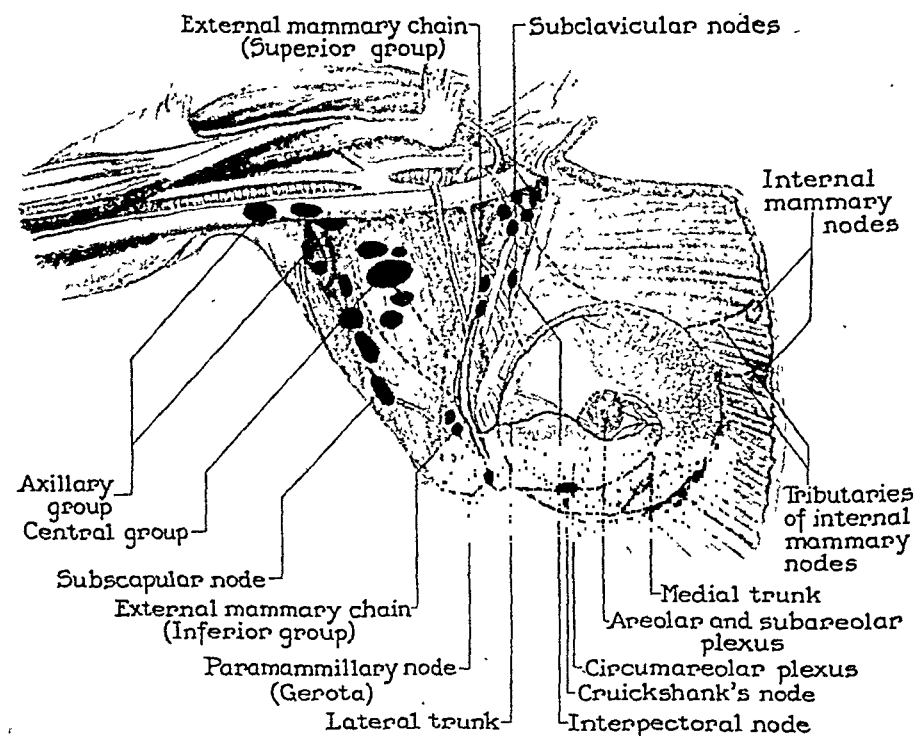


Fig. 1.—Lymphatics of the breast. (Adapted from Rouvière, *Anatomy of the Human Lymphatic System*. Translated by Tobias, Ann Arbor, 1938, Edwards Brothers, Inc.)

As in other regions of the body, the lymphatic system of the breast is composed of two elements: vessels and nodes. The cutaneous lymphatic vessels form a dense network lying in several planes in the areolar region. The most superficial of the areolar plexus is continuous with the lymphatics of the skin of the breast. Beneath this superficial plexus and connected with it is the subareolar plexus. This plexus receives the major portion of the lymphatics of the mammary gland.

The meshwork of lymphatics which is dense in the subareolar region thins out toward the periphery of the gland and in this location is

known as the circumareolar plexus. This plexus at its outer aspect is continuous with and has the same configuration as the lymphatics of the anterior thoracic wall.

The lymphatic trunks of the mammary gland proper arise in the inter- or perilobular network. Some of these vessels then follow the lactiferous ducts, receive lymphatics from them, and finally terminate in the subareolar plexus. Other lymphatic trunks do not enter the subareolar plexus but traverse the gland to its periphery where they emerge to terminate in the axillary nodes. Still other trunks run posteriorly with the perforating vessels to terminate in the internal mammary chain of nodes. Occasionally a trunk terminates directly in the transverse cervical chain of nodes.



Fig. 2 (Case 1) —Elevation of right breast and retraction of the nipple are well marked. The deformity produced by the tumor is visible on the 11 o'clock radius.

Two large collecting trunks, a medial and a lateral, connect the subareolar network with the axillary nodes, the former draining the upper aspect of the breast and the latter the lower part.

Lymph nodes are found in association with the lymphatic vessels and may be divided into three groups:

First, the small cutaneous nodes described by Cruikshank. These lie between the integument and the exterior surface of the mamma and are situated between the nipple and the axilla, in association with the collecting lymphatic trunks running to the axillary nodes.

Second, the nodes described by Kernisson. These are few in number but are consistently present, lying deep in the gland in association with the lymphatic trunks that follow the lactiferous ducts. To quote

Kermisson's description. "They are so intimately connected with the gland structures that at times it is difficult to decide whether a tumor is composed of mammary tissue itself or if it is formed from these nodes."

Third, the paramammary nodes described by Gerota which are not in the strict sense of the word mammary nodes. They do not lie in the gland but are situated just outside of it in the anterior abdominal wall.

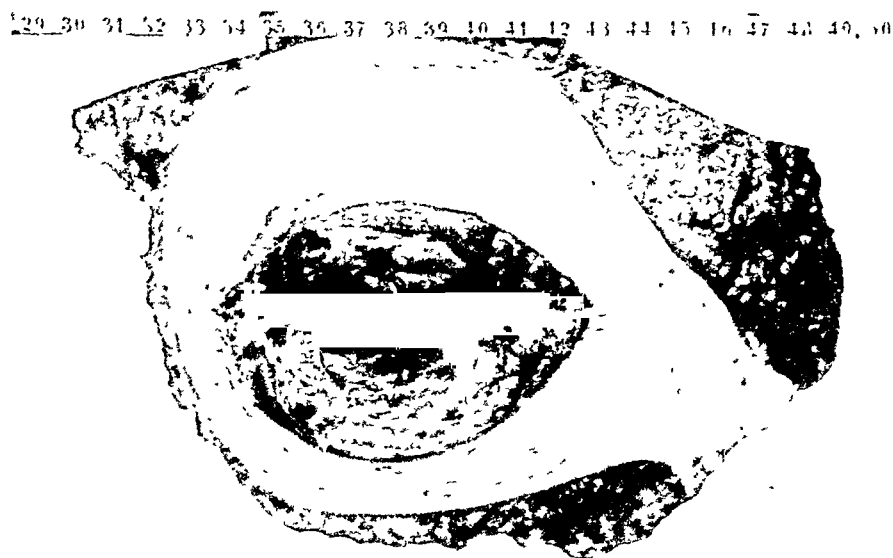


Fig. 3 (Case 1).—The tumor lies in the fat just below the skin and is well circumscribed.

*Description of Gross Specimen:* A fat breast with residue of thickened ducts. Prominently bulging the breast just below and external to the nipple was a large, freely movable, fairly soft, elastic, rubbery, circumscribed tumor measuring 6 by 5 by 5 cm. On section the tumor was soft, pinkish gray with areas of hemorrhage. In the axilla were several enlarged nodes which, however, consisted of a thick periphery of lymphoid tissue surrounding bulky fat lobules.

Since the breast commonly contains lymphoid infiltrates and some lymph nodes, the possibility of involvement of this organ by lymphosarcoma is readily explained. Secondary involvement by the disease is probably more common than a study of the literature would indicate. The breast is not usually sectioned routinely at autopsy so that localized disease in this organ, too small to give physical signs, may be easily overlooked.

Primary lymphosarcoma of the breast is an uncommon disease. In true primary lymphosarcoma of the mamma the disease arises here and remains localized a longer or shorter period of time. In order to establish this diagnosis there must be no evidence of the disease outside the breast. This is self-evident since the etiology of the disease and its mode of spread is unknown, although Willis believes it extends predominantly by lymphatic routes, spreading from node to node. Hence if two foci are

present at the initial examination (for example, a mass in the breast and enlarged ipsilateral axillary nodes), it cannot be determined which is the primary lesion. Similarly if a nodule is present in both breasts one may be primary and the other metastatic, unless the theory that the disease may be multicentric in origin is adopted.

The definition and classification of the manifestations of breast lymphosarcoma are important from the standpoint of treatment and prognosis. The following classification is proposed.

1. Primary lymphosarcoma of breast
  - A. Localized unilateral
    - (a) Single focus
    - (b) Multiple foci
  - B. Diffuse bilateral
2. Secondary lymphosarcoma of breast

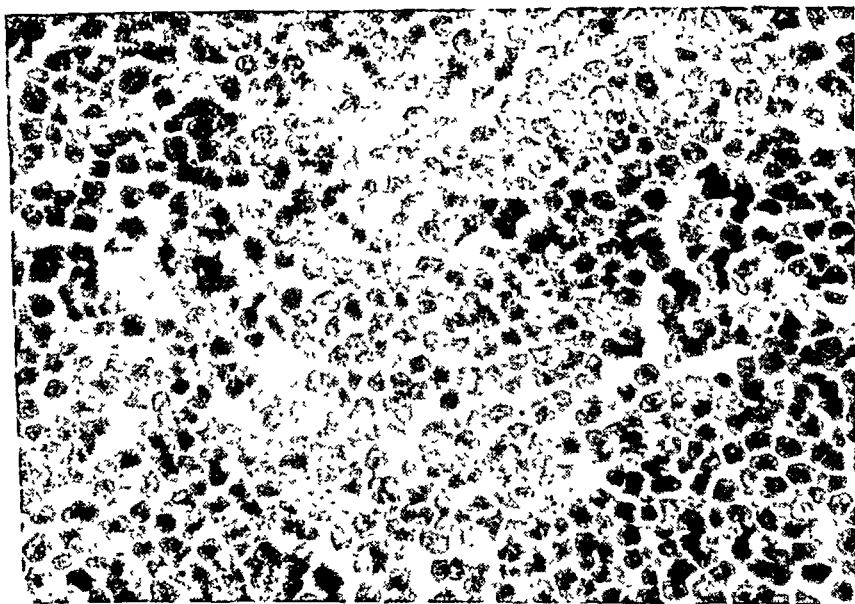


Fig. 4 (Case 1).—Reticulum-cell lymphosarcoma ( $\times 225$ ).

The diffuse type is an interesting condition. Cases have been reported by many clinicians (Pasqualino, Dellepiane, Billroth, Frascella). The majority of them occurred in young, pregnant Italian women, either nulliparas or multiparas, in their late twenties and early thirties. The condition, which is bilateral, manifests itself during the early months of pregnancy when the breasts enlarge quickly and soon reach a huge size. The enlargement may start simultaneously in both breasts or it may begin in one before the other.

Examination reveals huge, pendulous breasts in which the skin may be infiltrated, of a pinkish or violaceous hue, enlarged veins, and elevated surface temperature. The appearance is often similar to that



seen in carcinomatous skin infiltration. On palpation there is no tenderness but the mammae are hard and indurated. The axillary lymph nodes soon enlarge. The mammary glands, in the reported cases, weigh from 5 to 10 pounds each. Blood studies reveal nothing of importance except an occasional secondary anemia.

The disease is rapidly progressive, the outstanding symptoms being anorexia and weight loss. The patient usually goes through the pregnancy, is delivered of a normal baby, and dies within a few months after parturition. These breasts do not lactate. Autopsy reveals a disseminated lymphosarcomatosis.



Fig. 5 (Case 2).—The tumor is well circumscribed and does not invade the breast tissue ( $\times 45$ ).

*Description of Gross Specimen:* A radical mastectomy with skin ellipse measuring 26 by 11 cm. Near the center of the ellipse was a retracted nonulcerated nipple. When the breast was sectioned, in the lower portion of the upper outer quadrant a tumor nodule measuring approximately 2.5 cm. in diameter was found. It was lying approximately 4 cm. from the inner line of transection of the specimen and also was lying 3 cm. deep to the skin and approximately the same distance above the pectoral muscles. The bulk of the tumor on cross section was composed of soft, yellow-gray necrotic tissue. However, there was a rim of translucent gray, nodular, firm tumor tissue apparently still viable. The remainder of the breast tissue was firm and fibrous where it was not replaced by fat and no lobulations could be seen grossly. The ducts were not dilated but were surrounded by increased amounts of connective tissue. No grossly involved nodes were found in the axilla.

Ewing has raised the question, specifically in connection with the case described by Billroth, whether this condition is a variety of rapidly growing atypical carcinoma of pregnancy. The consensus of opinion, however, of those who have had an opportunity to study this disease is that it is lymphosarcoma.

There is a similar type of diffuse involvement of the breast seen in Hodgkin's disease.\* This, however, may be unilateral and is secondary to a generalized process.

\*To be published.

Localized lymphosarcoma of the breast is a rare condition. During the past twenty years 4,445 patients with benign tumor and 6,519 patients with malignant tumor were seen on the breast service of the Memorial Hospital. Of this total of 10,964 patients, only five had primary localized lymphosarcomas. One of these patients underwent a local excision of the tumor at another institution prior to admission to the Memorial Hospital clinic. The pertinent data of the five cases have been tabulated (Table I). A review of the literature discloses but two additional cases, that of Harrington and that of Fox, which satisfy the criteria for primary lymphosarcoma of the breast.

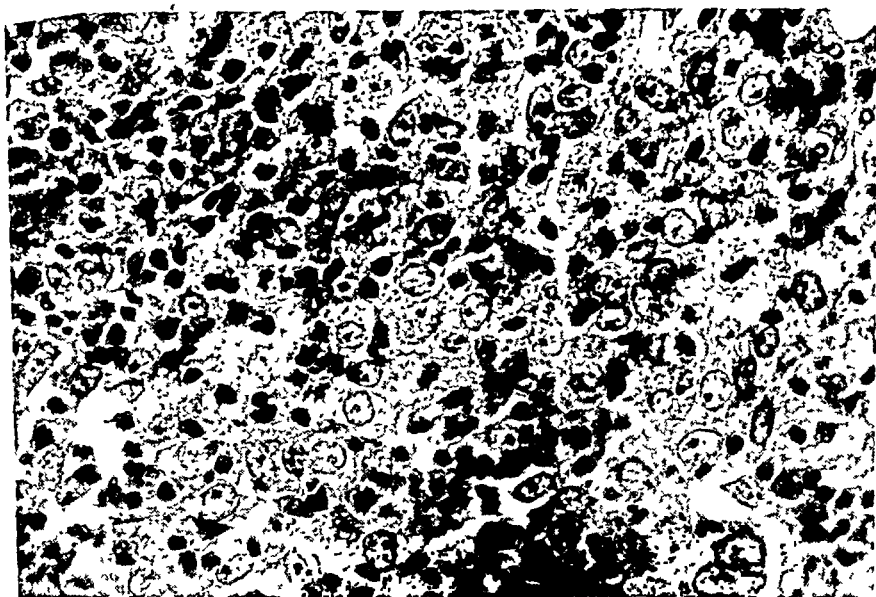


Fig. 6 (Case 2).—Higher magnification of the reticulum-cell lymphosarcoma shown in Fig. 5.—( $\times 225$ ).

Our series is much too small to permit of accurate conclusions. However, a few generalities will be attempted. The patients were white women in the fourth or fifth decade. Their average age was 50 years, 3 months. The elapsed time between the discovery of the tumor and the institution of therapy was short; from two to four weeks. The right breast was involved in four of the five patients. With the exception of one patient in whom the affected breast contained two lesions, the involvement occurred as a single focus of disease. The lesion was located in the upper outer aspect of the right breast in four of the patients. The mass in every instance was small, ranging in diameter from 1 cm. (the smallest) to 4 cm. (the largest). Of the four patients seen before operation there was nipple retraction in one and skin attachment or dimpling in three. X-ray studies of the chest were made in three patients and revealed an absence of pulmonary or medi-

TABLE I

CASE	(YR.) AGE	INITIAL SYMPTOM	DESCRIPTION OF BREAST	PAST HISTORY	PROVISIONAL DIAGNOSIS	ASPIRATION BIOPSY	GENERAL EXAMINATION	BLOOD	URINE	TREATMENT	PATHOLOGIC EXAMINATION	PROGRESS
1	53	Discovered painless mass in right breast two weeks before admission to hospital; some increase in size	Right breast, 4 cm. mass with skin attachment on radius of 11 o'clock near nipple; nipple retracted; no discharge	Gravida 1; para 1; menopause 2 yr. previously; nursed with left breast— never with right	Malignant tumor	Lymphomatous process	No lymphadenopathy or other evidence of disease; x-ray of chest negative	Hb., 75% R.B.C., 3.8 W.B.C., 13,600 Polys., 74 Large lymph., 4 Small lymph., 18 Trans., 3	Acid Albumin Sugar Many pus and R.B.C.	Radical mastectomy	Reticulum-cell lymphoma; nodes showed hyperplastic germinal centers but nothing which could be called lymphosarcoma	No evidence of disease of discase 7 yr. after operation
2	47	Discovered painless lump in left breast 1 week before admission to hospital; no increase in size; some pain in left chest radiating posteriorly	Left breast, 2 cm. mass, slightly tender on 11 o'clock radius 4 cm. beyond areola; suggestion of skin dimpling could be produced over it; left nipple slightly elevated, not stuck; no discharge	Menstrual 13 x 28 x 4-5; sister had carcinoma of breast	Cyst	Carcinoma, probably large cell medullary type with much lymphocytic infiltration	No lymphadenopathy or other evidence of disease; x-ray of chest negative	Not examined	Acid Albumin Sugar Occasional leucocytes	Radical mastectomy	Appeared to be primary mammary reticulum-cell sarcoma; nodes clear	No evidence of discase 3 yr. after operation

3	41	<p>Tell and bruised right breast 4 mo. previously; 2 mo. later noticed painless lump in the area which had been discolored; 1 mo. later lump excised at another hospital; diagnosis of lymphosarcoma made and patient referred to this institution for further treatment</p>	<p>Curved scar 3 cm. long, somewhat indurated, in right breast on radius of 8 o'clock just beyond areola</p>	<p>Gravida 4; para IV; nursed 3 infants; of breasts eaking during lactation; menstrual 17 x 28 x 3-4</p>		<p>No other evidence of disease; x-ray of chest negative; subse- quently developed slight yellowish discharge from left nipple which was diagnosed as duct stasis</p>	<p>Hb., 85% R.B.C., 4.3 W.B.C., 8,900 Segmented, 50 Lymph., 36 Monos., 3 Eos., 1 Mast cells, 1</p>	<p>Not examined</p>	<p>Radiation right breast laterally; 250 Kv., T.S.D. 50, field 8.5 x 25 cm., 30 M.A., 300 r. x 8, total 2400 r.</p>	<p>Submitted slide; consistent with lymphosarcoma</p>	<p>No evidence of disease 1½ yr. after operation</p>
4	53	<p>Discovered painless mass in upper outer quadrant right breast 2 weeks previous to admission to hospital</p>	<p>Right breast in upper outer quadrant, firm tumor 2.5 cm. in diameter with skin attachment and dimpling over it; superficial veins enlarged; no nipple retraction or palpable nodes</p>	<p>Gravida 1; para I</p>	<p>Malignant tumor; not sure whether lympho-sarcoma or carcinoma; former favored</p>	<p>No other evidence of disease; no chest x-ray taken</p>	<p>Not examined</p>	<p>Albumin Sugar 0 0</p>	<p>Radical mastectomy</p>	<p>Reticulum-cell sarcoma; nodes negative</p>	<p>No evidence of disease 3 mo. after operation</p>

TABLE I—CONT'D

CASE	AGE (YR.)	INITIAL SYMPTOM	DESCRIPTION OF BREAST	PAST HISTORY	PROVI- SIONAL DIAG- NOSIS	ASPIRATION BIOPSY	GENERAL EXAMINA- TION	BLOOD	URINE	TREATMENT	PATHOLOGIC EXAMINATION	PROGRESS
5	58	Painless lump in right breast for 3 weeks	Right breast, 2 firm, freely movable masses 1 cm. in diameter; 1 on the radius of 7 o'clock and other on that of 9 o'clock	Hysterec- tomy 13 yr. previ- ously fol- lowed by artificial meno- pause	Fibro- adeno- ma	Lymphoid tissue; in this loca- tion lym- phosarco- ma could not be ex- cluded	1 cm. node in right axilla; no chest x-ray taken	Hb., 75% R.B.C., 3.7 W.B.C., 8,400 No differ- ential	Albu- min Sugar	Local exci- sion fol- lowed im- mediately by simple mastec- tomy and low axillary dissection	Follicular lymphosar- coma (fol- licular and diffuse Brill- Symmers disease); there are lymphoid ag- gregates in the breast, although not in associa- tion with true breast tissue, and also in the axillary nodes	No evi- dence of dis- ease 6 mo. after opera- tion

astinal involvement. Blood studies, in the cases when they were carried out, gave normal findings.

All of the patients, with the exception of the one who underwent a local excision of the tumor at another clinic, were treated exclusively by surgery. The procedure in three was a radical mastectomy and in the fourth a simple mastectomy with a low axillary dissection. The patient whose tumor had been locally excised previous to consultation at this clinic was treated with high voltage x-ray applied to the area of excision. The axilla was not radiated.

The pathologic report was reticulum-cell sarcoma in three of the patients operated on and follicular lymphosarcoma (Brill-Symmers' disease) in the fourth. The slide submitted from the case in which the tumor was excised at another clinic was interpreted as "consistent with lymphosarcoma." No axillary node involvement was found in any patient. In two of the patients (Cases 4 and 5) the pathologist's description of the gross findings was very suggestive that the process had its inception in the nodes described by Cruikshank. The description of these gross specimens is given with the respective photomicrographs (Figs. 8 to 11). All the pathologic studies were made by Dr. Fred Stewart and his associates.

The protean nature of the lesion may be judged from the provisional diagnoses which were carcinoma, malignant lesion, cyst, and fibro-adenoma. The various conditions which must be considered in a differential diagnosis and the diagnostic criteria are given in Table II. The only points suggestive of diagnostic significance are that the mass occurred in the upper outer quadrant of the right breast in four of our five patients, and that the mass in every instance was small, less than

TABLE II  
DIFFERENTIAL DIAGNOSIS OF BREAST NODULES

DISEASE	PRESUMPTIVE EVIDENCE	CONCLUSIVE EVIDENCE
Carcinoma	Skin attachment; nipple retraction	Biopsy
Cyst	Transillumination; fluctuation	Aspiration
Leucemia	Generalized lymphadenopathy	Blood picture
Primary lymphosarcoma	Small mass in upper outer quadrant; 4th or 5th decade of life	Biopsy
Secondary lymphosarcoma	Generalized lymphadenopathy	Biopsy
Hodgkin's disease	Generalized lymphadenopathy	Biopsy
Sarcoma	Rapidly growing; large size	Biopsy
Chloroma	Generalized lymphadenopathy; osseous changes	Green color on section
Tuberculosis	Pulmonary tuberculosis; sinus tract	Biopsy

4 cm. in diameter. The latter finding may be due to the fact that the lesions were discovered early. These criteria are of little differential diagnostic value since carcinoma occurs frequently in that location, in the same age group, and with the same characteristics. That the condition may closely simulate carcinoma is exemplified by the circumstance that this was the provisional diagnosis in two of the patients in the present series. In cases reported by Ghon and Roman and by Clairmont, the patients underwent a radical mastectomy for supposed carcinoma of the breast which subsequently was proved to be lymphosarcoma. A post-mortem examination revealed a large mediastinal tumor as part of a widespread abdominal lymphosarcomatosis.

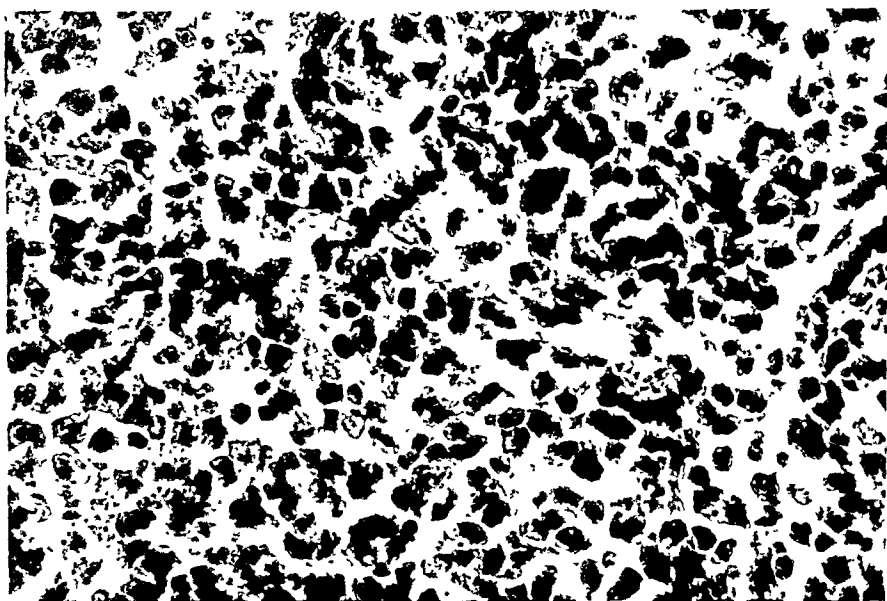


Fig. 7 (Case 3).—Lymphosarcoma ( $\times 225$ ).

This type of error can be avoided by a preoperative chest x-ray. A mediastinal mass is suggestive of lymphoma or metastatic carcinoma, either of which is a contraindication to surgery. The blood examination is also important as a diagnostic aid in breast nodules caused by leucemia or chloroma. In the ultimate analysis the correct diagnosis can be made only when the tumor is removed and examined microscopically, although the aspiration biopsy findings were suggestive of a lymphomatous process in every one of our patients.

Primary lymphosarcoma of the breast, like that of the stomach, is a distinct entity. This form of the disease may be of lower-grade malignancy than generalized lymphosarcoma and may tend to remain localized for a considerable period of time. For that reason early recognition is important since the disease is amenable to surgery in its localized phase. Gall has recently published a series of forty-eight cases of lymphoma of different organs and structures in which the

patients were treated by surgery with an average survival period of 5.2 years. This figure is about double that obtained by other methods of treatment in similar cases.

Three of our patients were treated by radical mastectomy and are alive and free of disease seven years, three years, and six months, respectively. One patient was treated by local excision of the lymphomatous nodule followed by deep x-ray therapy and is alive and free from disease one and one-half years after the surgical procedure. In one patient a simple mastectomy with low axillary dissection was performed. This patient is alive and free from disease three months following operation.

A survey of the reported cases of lymphosarcoma of the breast in which the patients were treated by surgery (Seidemmann, Ghon and Roman, Clairmont, Finsterer, Kundrat, D'Aunoy and Wright, Schreiner and Thibaudeau, Fox, Hill and Stout, and Harrington and Miller) re-

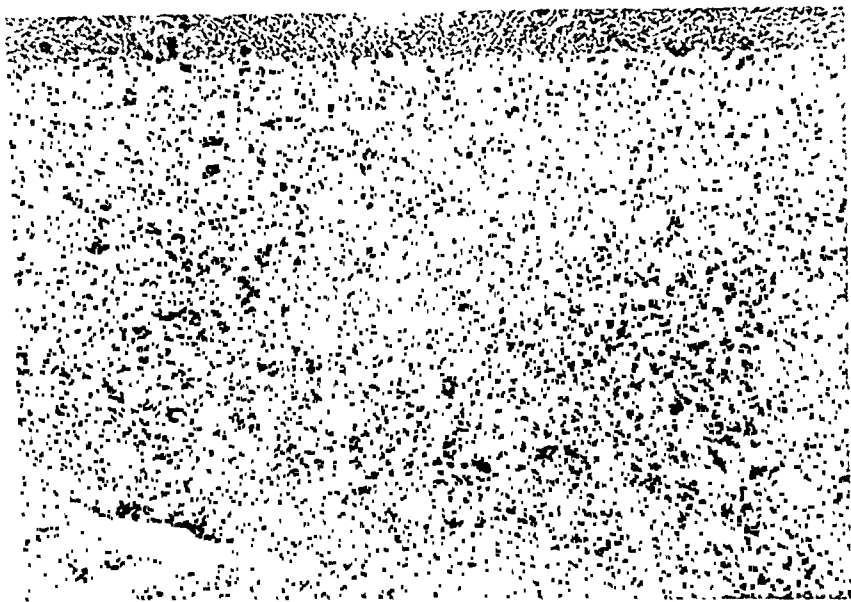


Fig. 8 (Case 4).—Reticulum-cell lymphosarcoma, low magnification (X45).

*Description of Gross Specimen:* Moderate-sized radical mastectomy of the right side. Five centimeters from the nipple was an area of skin dimpling. Beneath this area of skin alteration a not too well-defined but firm tumor could be felt. On section the central portion of this tumor lay 7 cm. from the base of the nipple. The tumor lay in the fat and connective tissue which separated the skin from the underlying breast tissue. On first glance there was a fleeting impression that the tumor was lipomatous but after complete section this false appearance was seen to be due to the fact that the tumor at its periphery merged almost imperceptibly with the lobules of fat. The tumor measured about 5 cm. with the bulk of the tumor being about 3.5 cm. It was well demarcated, since there were peripheral extensions into the surrounding fat. After section the tumor did not feel firm but was of the consistency of fat. The part of the tumor had the fish-fleshlike appearance of lymphoid tissue. The breast tissue showed but little fat replacement. There was moderate dilation of most of the larger mammary ducts and they contained creamy yellowish material. Not a single cyst was seen and no other lesions were grossly visible. The mammary lobules were fairly numerous and seemed rather small. In summary, the breast tissue was unusually homogeneous. Eighteen nodes were dissected from various areas in the axilla. These were pea sized or slightly larger save for one node which was 1.5 cm. in diameter. This node was slightly firm at one point near its capsule but definite structural alteration was not seen.



reveals that with the exception of the patient of Harrington and that of Schreiner, none survived more than a few months. Schreiner's patient had palpable nodes in the right axilla at the time the right radical mastectomy was performed. Although she soon developed widespread metastases, these were controlled by irradiation for a period of almost five years, after which there is no record. Harrington's patient was alive and free of disease six years after radical mastectomy. D'Aunoy gives no information relative to his patient's postoperative course, and Hill's patient was followed for only four months. All of the other patients retrogressed rapidly, death apparently being hastened by the operation. An analysis of these cases reveals that, with the exception of one of Harrington's patients and one of Fox's, in no instance do they

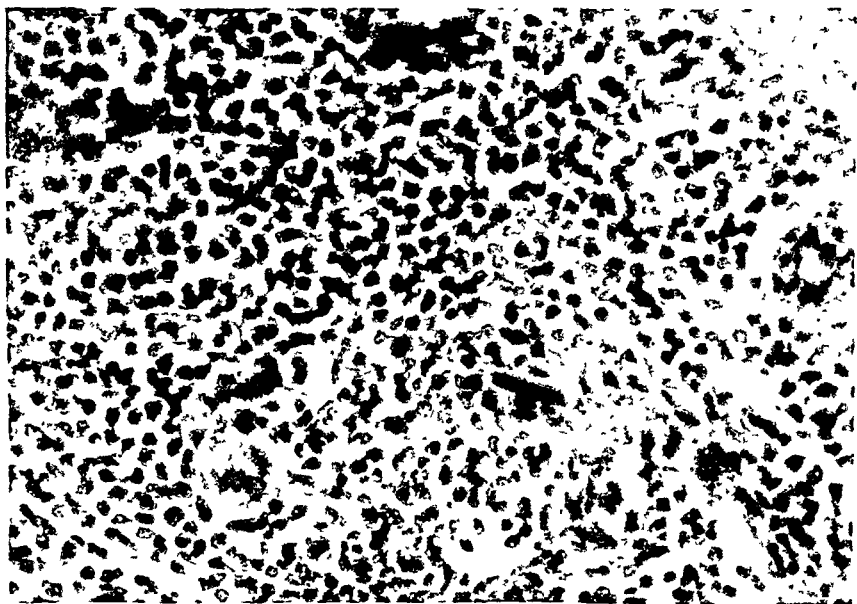
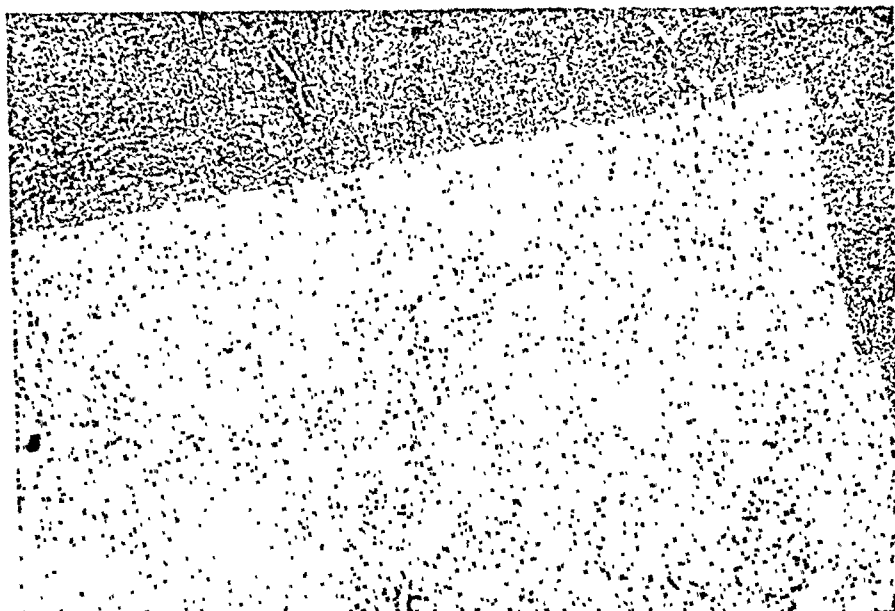


Fig. 9 (Case 4).—Higher magnification of a portion of the field shown in Fig. 8 ( $\times 225$ ).

satisfy the foregoing criteria given for primary lymphosarcoma. At the time of the first examination all of these other individuals presented more than local evidence of the disease. In some instances they gave a history of a primary nodule in the breast, but since no examination was made at that time, the history alone was not reliable.

On the basis of the foregoing facts it would seem that lymphosarcoma of the breast should be treated by surgery only if the disease is localized in the breast and confined to one breast. Impressed by the gratifying results from surgery of primary localized lymphosarcoma in other parts of the body, notably the gastrointestinal tract, we believe this mode of therapy to be effective. Our patient who lived



Fi

Atypical follicles are

The excised breast tissue revealed the presence of a nodule about 1 cm. in diameter, rather soft in consistency, which showed a homogeneous yellowish surface which had the appearance of lymphoid tissue. The nodules were definitely not in the node-bearing axilla, neither were they in the breast proper but in the subcutaneous fat overlying the breast tissue.

The breast itself showed nothing of note. Several enlarged nodes were encountered in the axilla at all levels, varying between 8 mm. and 3 cm.

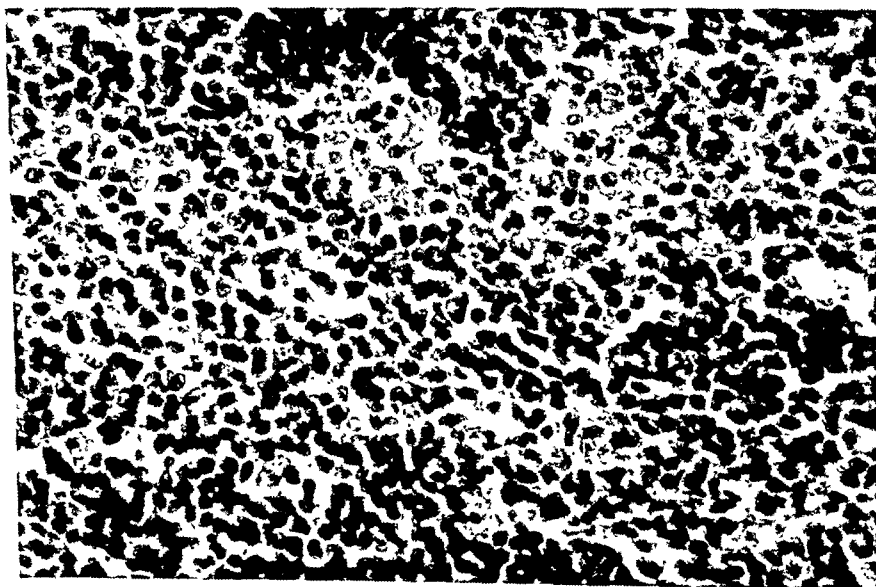


Fig. 11. (Case 5).—Follicular lymphosarcoma ( $\times 70$ ). This is a higher magnification of a portion of a follicle shown in Fig. 10.

seven years and that of Harrington tend to support this view. The other cases in our series are too recent to be of value in basing conclusions.

If there is other evidence of disease in addition to that in the breast, then surgery is contraindicated and the patient is best treated as a case of generalized lymphosarcomatosis. Whether the prognosis in the cases of multiple nodules in the same breast is different from that in which the lesion is solitary cannot be determined from this small group. Only one of the patients in the present series had multiple foci in the breast. This patient is free from evidence of disease one-half year after her simple mastectomy.

#### SUMMARY AND CONCLUSIONS

1. Primary lymphosarcoma of the breast is a rare lesion.
2. A classification of breast lymphosarcoma is proposed.
3. The lymphatic system of the breast and its correlation with lymphosarcoma are described.
4. Five cases of primary breast lymphosarcoma are reported, in which all the patients are alive and free from disease following surgery for periods ranging from seven years to three months.
5. We believe that in primary lymphosarcoma of the breast, as in primary gastrointestinal lymphosarcoma, radical surgery is the procedure of choice.
6. Criteria for operability are set forth.

#### REFERENCES

1. Baumgartner, A.: *Maladie de la Mammelle. Nouveau Traité de Chirurgie*, Paris, 1913, Le Dentu et Delbet, p. 323.
2. Billroth, L.: *Handbuch der Frauenkrankheiten*, vol. 3, Stuttgart, 1877-1880, F. Enke.
3. Clairmont, P.: Einige Fälle von Seltenen Geischwulstmatastasen, *Arch. f. klin. Chirg.* 89: 513, 1909.
4. Cruikshank, W.: *Anatomy of the Absorbing Vessels of the Human Body*, ed. 2, London, 1790, J. Nicol.
5. D'Aunoy, R., and Wright, R.: Sarcoma of the Breast, *Ann. Surg.* 92: 1059, 1930.
6. Dellepiane, G.: Linfoblastoma bilaterale della mammella simulante una ipertrofia mammaria gravidica, *Riv. ital. di ginec.* 11: 162, 1930.
7. Duany, N. P.: Linfosarcoma de las glandulas mammarias, *Bol. Liga contra el cáncer* 16: 65, 1941.
8. Elsberg, C. A.: Multiple Lymphosarcoma of Both Breasts, *Ann. Surg.* 60: 767, 1914.
9. Ewing, J.: *Neoplastic Diseases*, ed. 4, Philadelphia, 1940, W. B. Saunders Co., p. 557.
10. Finsterer, J.: Ueber das Sarkom der weiblichen Brüstdrüse (Case 23), *Deutsche Ztschr. f. Chir.* 86: 352, 1907.
11. Fox, S.: Sarcoma of the Breast, *Ann. Surg.* 100: 401, 1934.
12. Frascella, P.: Linfoblastomastosi sistemica mammaria simulante una ipertrofia patologica gravidica, *Tumori* 10: 343-360, 1924.
13. Gall, E. A.: The Surgical Treatment of Malignant Lymphoma, *Ann. Surg.* 118: 1064, 1943.
14. Geist, S., and Wilensky, A.: Sarcoma of the Breast, *Ann. Surg.* 62: 11, 1915.
15. Gerota, D.: Cited by Rouvière, H.: *Anatomy of the Human Lymphatic System*, translated by Tobias, M. J., Ann Arbor, 1938, Edwards Brothers, Inc., p. 129.

16. Ghon, A., and Roman, B.: Ueber das Lymphosarkom (Case No. 8), Frankfurt. Ztschr. f. Path. 19: 1, 1916.
17. Gross, S. W.: Tumors of the Mammary Gland, New York, 1880, Appleton & Co.
18. Halsam, W.: *Birmingh. M. Rev.* 25: 286, 1889.
19. Harrington, S. W., and Miller, J. M.: Lymphosarcoma of the Mammary Gland, *Am. J. Surg.* 48: 346, 1940.
20. Heineke, H.: Experimentelle Untersuchungen über die Einwirkung der Röntgenstrahlen auf das Knochenmark nebst einigen Bemerkungen über die Röntgentherapie der Leukämie und Pseudoleukämie und des Sarcoms (Case No. 3), *Deutsche Ztschr. f. Chir.* 78: 197, 1905.
21. Hill, R., and Stout, A.: Sarcoma of the Breast, *Arch. Surg.* 44: 723, 1942.
22. Kermisson, E.: *Bull. de la Soc. Anat. de Paris*, 4e Serie 7: 453, 1882.
23. Kundrat, Prof.: Ueber Lympho-Sarkomatosis, *Wien.-klin. Wchnschr.* 6: 211, 1893.
24. McWilliams, C. A.: Bilateral Lymphosarcoma of the Breasts, *Ann. Surg.* 55: 439, 1912.
25. Pasqualino, G.: Linfoblastoma bilaterale delle mammelle, *Tumori* 18: 172, 1932.
26. Schoen, R.: Lymphosarkomatose mit Beiteiligung der Brüste bei einem Gynäkomasten, Frankfurt. Ztschr. f. Path. 25: 112, 1921.
27. Schreiner, B., and Thibaudeau, M.: Sarcoma of the Breast, *Ann. Surg.* 95: 433, 1932.
28. Seidemann, H.: Seltener Mammatumor, *Monatschr. f. Geburtsh. u. Gynäk.* 78: 310, 1928.
29. Willis, R.: *The Spread of Tumors in the Human Body*, London, 1934, J. & A. Churchill, Ltd., p. 38.

## MIXED MALIGNANCY OF THE BREAST

### CASE REPORT OF A COMBINED CARCINOMA AND SARCOMA IN A CHILD, WITH REVIEW OF THE LITERATURE

H. G. SMITHY, M.D., CHARLESTON, S. C.

*(From the Departments of Surgery of The Medical College of the State of  
South Carolina and Roper Hospital)*

THE simultaneous occurrence of two different malignant processes at points of origin quite distinct and separate from each other is a well-established entity. The papers of Wells,<sup>1</sup> Loeb,<sup>2</sup> Major,<sup>3</sup> and others<sup>4-6</sup> indicate that multiple primary malignant tumors are not rare. Much less common than these anatomically unrelated tumors is the presence of two different types of neoplastic tissue growing within the same organ.

Mixed malignancy of the breast can be divided into two categories: (1) the simultaneous presence of two distinct varieties of malignant tumors growing side by side but having no structural intermingling of their elements, and (2) a combination growth of two different malignant tissues whose component parts are intimately blended with one another into a single tumor.

The first type may be regarded as a coincidental occurrence of two independent neoplasms in the same organ. Kettle<sup>7</sup> and Curphey<sup>8</sup> each reported one case of fibrosarcoma and invasive carcinoma of the breast, the malignant elements existing as separate tumors and showing no structural intermingling. In a case recorded by Schwarz,<sup>9</sup> the patient was operated upon for carcinoma of the left breast; three years later she developed a sarcoma in the right breast which also showed metastatic carcinoma from the original tumor, apparently unrelated to the sarcoma. A similar instance was reported by Lester,<sup>10</sup> in which radical mastectomy for cancer was followed in fifteen months by recurrence of the epithelial tumor in the scar, associated with a neurogenic sarcoma. The simultaneous occurrence of these two tumors was regarded as coincidental.

The second type of mixed tumor of the breast can hardly be considered as an accidental coexistence of different neoplastic lesions. Intimate association of both epiblastic and mesoblastic components, homogeneously blending into a single tumor, is probably more than accidental. It appears likely that these tumors either arise from a single cell, or one element occurs first and subsequently stimulates proliferation of the other. Experimentally, the appearance of malignant stroma in a previously pure carcinoma has been demonstrated in

mice. Ehrlich and Apolant,<sup>11</sup> Haaland,<sup>12</sup> and Russell<sup>13</sup> independently established beyond doubt the metaplastic property of mammary connective tissue in which adenocarcinoma is growing. In the tenth generation transplants of breast cancer in mice, Ehrlich and Apolant obtained a malignant tumor which exhibited sarcomatous properties as well as the original epithelial element. Russell's animals showed a similar change in which previously normal connective tissue stroma cells were gradually transformed into malignant sarcoma cells. About fifty-five days were required for this process to complete itself and, once the sarcoma became established, further propagation of the tumor resulted in complete elimination of the carcinoma with persistence of a pure sarcoma. In an exhaustive study of the problem, Haaland observed the same tissue transformation in transplanted breast tumors of mice. The reverse of this phenomenon has been reported by Nicholson.<sup>14</sup> In 1912, he inoculated the breast of a white female rat with sarcomatous tissue. Growth of a pure sarcoma occurred but, after reaching its maximum size, the tumor was seen to shrink. The excised specimen showed death of the sarcoma, while in its place a small malignant epithelial neoplasm had appeared. The origin of the carcinoma was thought by Nicholson to be from the lining of a sinus produced by his inoculation, an epithelial implant having been pushed into the deeper tissues by the needle. These experimental observations lend support to the possibility that a malignant lesion of epiblastic origin can stimulate adjacent mesoblastic elements to proliferate, and vice versa. Concerning the possibility that combination growths can originate from a single cell, widely divergent opinions prevail among pathologists so that no positive expression can be made at this time.

Classification and nomenclature of dual tumors of the breast are difficult and confusing because of the uncertainty regarding their etiology. Generally, they have been called either carcinosarcoma or sarcocarcinoma, depending upon which tissue element predominates in the microscopic sections. Harrington and Miller<sup>15</sup> proposed that mixed malignant lesions be designated according to the observer's conception as: (1) mixed growths or malignant teratomas, (2) carcinoma with secondary sarcoma, (3) sarcoma with secondary carcinoma, (4) carcinoma and sarcoma.

Tables I and II comprise a summary of the literature of thirty-two cases, reported by thirty authors, of breast tumors composed of more than one malignant element. Table I includes twenty-two cases of true mixed tumor wherein the neoplastic components are intimately blended with one another. Table II represents ten cases in which the individual malignant tissues are not intermingled but coexist simultaneously as independent tumors within the same breast. This review includes only those cases in which the tumor elements were composed of sarcoma and mammary carcinoma. All patients reported were

TABLE I

AUTHOR	DATE	AGE OF PA- TIENT (YR.)	TYPE OF NEOPLASM	METASTASES
Dorsch <sup>20</sup>	1896	43	Carcinoma and spindle-cell sarcoma; malignant elements blended	N. G.*
Kerberiou and Danel <sup>21</sup>	1897	55	Carcinoma and myxosarcoma; slight blending of malignant elements	Carcinoma only; axillary nodes
Schlagenhauer <sup>23</sup>	1906	50	Carcinoma and giant-cell and spindle-cell sarcoma, partially blended	Both malignant elements, axillary nodes
Krompecher <sup>24</sup>	1908	36	Carcinoma and giant-cell sarcoma; intimate blending of both malignant elements	N. G.
Orth <sup>25</sup>	1910	40	Carcinoma and sarcoma intimately blended	N. G.
Pfeiffer <sup>26</sup>	1910	71	Carcinoma and spindle-cell sarcoma; intimate blending of both malignant elements	Carcinoma only; axillary nodes
Coenen <sup>27</sup>	1910	43	Carcinoma and spindle-cell sarcoma; intimate blending of both elements	Carcinoma only; axillary nodes; postoperative recurrence at 5 mo. of sarcoma only in axillary nodes
Secousse <sup>28</sup>	1912	67	Carcinoma and fibrosarcoma; intimate blending of both elements	N. G.
Waelle <sup>30</sup>	1913	50	Chondrosarcoma and carcinoma; blending of malignant elements	N. G.
Takano <sup>31</sup>	1914	49	Carcinoma and spindle-cell sarcoma; intimate blending of both types of neoplastic tissue	Carcinoma only; axillary nodes
Wehner <sup>32</sup>	1915	41	Spindle-cell sarcoma, scirrhus carcinoma, and squamous-cell epithelioma; intimate blending of all elements into "true mixed tumor"	N. G.
Hedrén <sup>34</sup>	1915	42	Spindle and giant-cell sarcoma and carcinoma; intimate blending of both malignant elements	None found
Harbitz <sup>35</sup>	1916	*	Giant-cell sarcoma and carcinoma; intimate blending of both malignant elements	N. G.
Wilensky <sup>36</sup>	1919	48	Round- and spindle-cell sarcoma intimately blended with carcinoma	N. G.
Kunsmüller <sup>37</sup>	1920	73	Spindle-cell sarcoma and carcinoma; intimate blending of both malignant elements	Sarcoma; lungs, pleura and ribs; no carcinoma
Jessup <sup>38</sup>	1923	34	Giant- and spindle-cell sarcoma intimately blended with carcinoma	Carcinoma only; axillary nodes
Kreibig <sup>39</sup>	1925	52	Case II, cylindrical and epidermoid carcinoma and spindle-cell sarcoma, intimately blended	Carcinoma only; axillary nodes
Biehl <sup>40</sup>	1927	62	Case I, round-, spindle-, and giant-cell sarcoma and carcinoma; intimate blending of elements	Original, none; postoperative recurrence in scar at 5 mo., of pure sarcoma

\*N. G., Not given in original report.

TABLE I.—CONT'D

AUTHOR	DATE	AGE OF PA- TIENT (YR.)	TYPE OF NEOPLASM	METASTASES
Helwig <sup>41</sup>	1927	43	Carcinoma and giant-cell sarcoma intimately blended throughout breast	Both carcinoma and sarcoma, axillary nodes; postoperative recurrence in scar at 3 mo. of both elements
Kückens <sup>42</sup>	1928	48	Carcinoma and spindle-cell sarcoma; intimate blending of both malignant elements	N. G.
Pasternack and Wirth <sup>43</sup>	1936	60	"Adenoma acanthoma sarcomatodes," epidermoid carcinoma intimately blended with sarcomatous stroma; independent adenocarcinoma surrounded by normal stroma; no blending with other malignant elements	None found
Harrington and Miller <sup>15</sup>	1940	50	Spindle- and giant-cell sarcoma and carcinoma; intimate blending of both malignant elements	None found

women, no recorded instance being found of mixed carcinoma and sarcoma in the male breast. Not included in the collected cases are mixed breast tumors of sarcomatous and epidermoid carcinomatous composition. For detailed information about this variety of neoplasm the papers of Bouchut and Martin,<sup>16</sup> Lecène,<sup>17</sup> DeBoucaud and Pierre-Nadal,<sup>18</sup> and Cornil<sup>19</sup> may be consulted.

#### CASE REPORT

CASE 1 (Roper Hospital Case No. 111954).—A 10-year-old Negro girl entered the hospital Aug. 8, 1940, complaining of an enlargement of the left breast. Her mother stated that the patient developed a swelling within the affected breast "about the size of an egg" when she was 2 years old, the mass spontaneously disappearing within six months. The child experienced no further difficulty until five months prior to admission, at which time the same breast began to enlarge diffusely. Increase in size continued until, at the time of hospitalization, the breast resembled that of a fully developed young adult woman. There was no pain or tenderness of the affected breast and no history suggesting an inflammatory process. On a previous occasion, three months before admission, there occurred a white discharge from the nipple which persisted for only a day. No other nipple discharge of any sort was noted. The right breast remained undeveloped and was at no time a source of complaint. The child never had menstruated. The remaining history of her systems was normal. The mother thought that some weight loss had occurred but was uncertain of the amount. The family history revealed no known evidence of cancer and no other pertinent data. The past history included measles and chicken pox but revealed no organic ailments. Growth and development since birth had been normal.

Physical examination on admission showed a normally developed, fairly well-nourished girl. Temperature was 99° F.; blood pressure, 114/68; pulse, 100 per minute. The left breast was diffusely enlarged, measuring 11 by 9 cm., while



TABLE II

AUTHOR	DATE	AGE OF PA- TIENT (YR.)	TYPE OF NEOPLASM	METASTASES
Gould <sup>22</sup>	1901	56	Largely spindle-cell sarcoma; separate, independent growth of scirrhus carcinoma	N. G.*
Kettle <sup>7</sup>	1912	46	Separate neoplasms of carcinoma and fibrosarcoma blended only at point of contact of the two tumors	Original not given; postoperative recurrence at 3 yr. with generalized metastases of carcinoma only
Perrier <sup>29</sup>	1912	60	Spindle and giant-cell sarcoma and carcinoma; no intimate blending of elements	N. G.
Schwarz <sup>9</sup>	1913	50	Metastatic carcinoma (from opposite breast) associated with independent sarcoma; no blending	Carcinoma only; axillary nodes
Kennedy and Case <sup>33</sup>	1915	46	Carcinoma and spindle-cell sarcoma existing as separate independent tumors; no blending of elements	Carcinoma only; axillary nodes
Kreibig <sup>39</sup>	1925	50	Case 1, carcinoma and osteosarcoma growing independently; no blending of malignant elements	Carcinoma only; axillary nodes
Biehl <sup>40</sup>	1927	55	Case 2, polymorphic giant-cell sarcoma and medullary carcinoma existing as adjacent but separate independent neoplasms; no intermingling	None found
Lester <sup>10</sup>	1931	50	Postoperative recurrence in scar at 15 mo. of carcinoma associated with neurogenic sarcoma; independent, unrelated tumors with no blending of malignant elements	N. G.
Curphey <sup>8</sup>	1935	33	Carcinoma and spindle-cell sarcoma existing as adjacent, independent growth; no blending of malignant elements	Carcinoma in liver; no sarcoma
Mondor, Gauthier-Villars, and Gottesmann <sup>44</sup>	1936	49	Carcinoma and spindle-cell sarcoma in contact with each other but existing as separate unblended tumors	None found

\*N.G., Not given in original report.

the right breast and nipple were normal. On palpation, the enlarged breast was found to be firm, somewhat elastic, and lobulated. The excess mammary tissue was not attached to the chest wall or to the overlying skin. Mobility of the entire breast was free in all directions, and there was no retraction of the nipple or its areola. There were numerous small discrete, firm, movable lymph nodes in the left axilla. One in particular was considerably larger than the others. Discretely enlarged lymph nodes were also noted in the opposite axilla, in the neck, and in both inguinal regions. Aside from marked hypertrophy of the tonsils, no other abnormalities were noted.

Routine laboratory studies of the urine and blood were normal. The blood Wassermann and Kline tests were negative. X-ray studies of the chest, vertebral column, and long bones showed no abnormalities and there was no radiographic

evidence of pituitary tumor. The basal metabolic rate was minus 16 per cent. A Friedman modification of the Aschheim-Zondek reaction was negative.

It was felt that enlargement of the affected breast was due to simple hyperplasia, possibly of endocrine origin, although no specific disorders of the endocrine system could be found. Accordingly, a simple mastectomy was done through transverse elliptical incisions, and the entire breast removed, along with the largest of the axillary lymphoid masses, which was readily accessible near the lateral end of the operative wound. The entire mammary mass appeared to be encapsulated and was quite easily stripped from the underlying pectoral fascia. An axillary dissection was not done. Postoperative convalescence was uneventful.

*Pathologic Description.*—Microscopic sections of the breast revealed a highly malignant connective tissue neoplasm of spindle-cell type. The cellular elements were arranged in swirling bands (Figs. 1 and 2) and varied in appearance from slender, elongated structures to broad, anaplastic, ribbonlike masses of cytoplasm



Fig. 1.—Bands of spindle cells arranged about atypical glandular elements ( $\times 200$ ).

(Fig. 3). The large ovoid and spindle-shaped nuclei showed a pronounced hyperchromatic character. Tumor giant cells and atypical mitotic figures were numerous and emphasized the high grade of malignancy (Figs. 3 and 4). Scattered throughout the tumor were many branching glandular elements of atypical appearance. Hyperplasia of the lining epithelium was well defined and papillary ingrowth was a prominent feature (Figs. 1 and 2). In spite of this proliferative activity, there was no specific evidence in the many sections taken from the breast tissue itself that the epithelial portion of the tumor was malignant, although a few mitotic figures were seen among the reduplicated epithelial cells. Sections of the removed axillary node, however, showed invasion of the lymphoid tissue in its subcapsular zone by the same glandular elements noted in the primary tumor, but none of the sarcomatous element was found.\* Their anatomic arrangement was typical of early metastatic adenocarcinoma, the parent glandular structure being maintained intact. The histologic diagnosis was spindle-cell sarcoma and adenocarcinoma with early metastases of the carcinomatous element to the axillary lymph nodes.

\*Sections of the lymph node are not available for photomicrographs.

*Postoperative Course.*—Shortly after operation, deep x-ray therapy was begun. The patient received a total of 9,000 R (measured in air), administered to six fields over a period of six weeks. Ten months after operation, she was readmitted to the hospital for study. Her progress had been highly satisfactory and she had

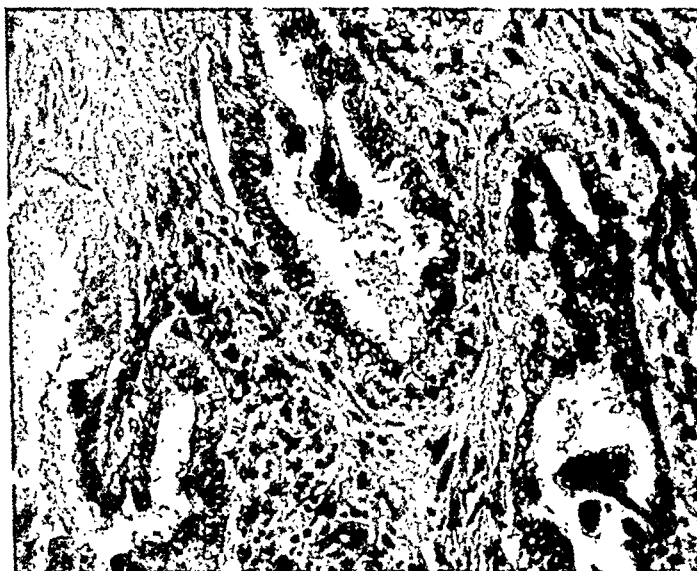


Fig. 2.—Glandular elements showing marked hyperplasia of the epithelium with papillary invaginations ( $\times 300$ ).

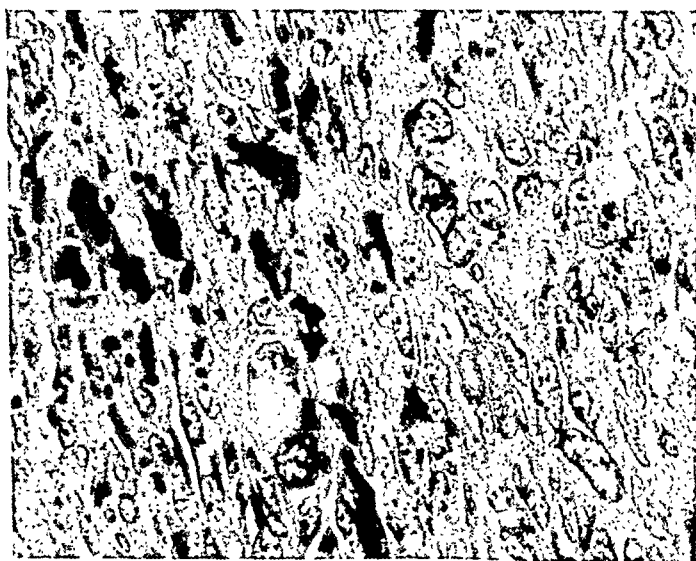


Fig. 3.—Large nuclei, tumor giant cells, and broad anaplastic chromatin masses of the mesoblastic component ( $\times 500$ ).

led a normal, uneventful existence. Radiologic studies of the lungs, thoracic cage, vertebral column, and long bones showed no evidence of metastatic malignancy. The operative scar was soft and pliable and freely movable over the chest wall. Developmental changes of puberty were noted and appeared quite normal, but the patient had not menstruated to this time. Her weight was 91 pounds. In August,

1942, two years after operation, further roentgenologic studies of the chest and vertebral column were found to be entirely normal. In March, 1943, thirty-one months postoperative, the patient was seen again. Menstruation had begun the previous month (at the age of 12½ years). As on previous occasions, the history and physical examination revealed no abnormalities and her condition appeared to be excellent; weight was 99 pounds. In November, 1943, three years and three months postoperative, correspondence from the child's mother stated that the patient was "getting along fine" and reported her weight as 103 pounds. A similar report was received in June, 1944, three years and ten months postoperative, stating that the child weighed 110 pounds and that her health was excellent.

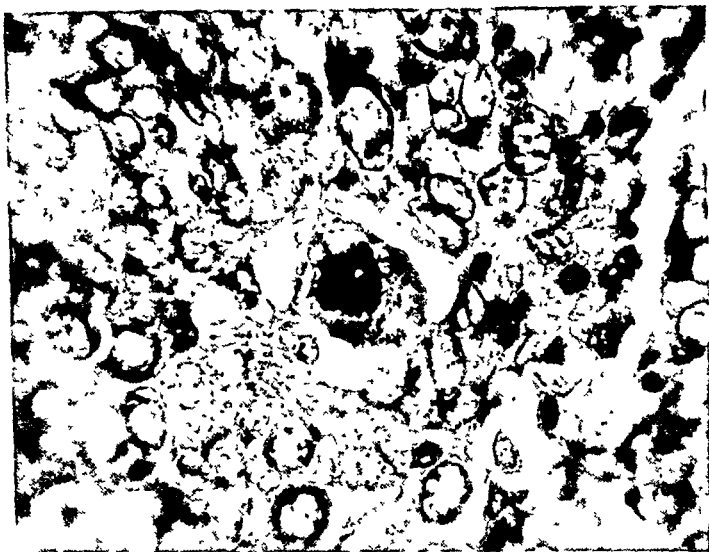


Fig. 4.—Large atypical mitotic figure of the sarcomatous element ( $\times 750$ ).

#### DISCUSSION

Consideration of the foregoing case focuses attention on the following points of interest: (1) the nature of the tumor, (2) the age of the patient, and (3) the method of treatment.

Regarding classification of the tumor, it is desirable to avoid such terms as carcinosarcomatodes, carcinosarcoma, and sarcocarcinoma which have been employed to indicate the relative time of appearance of the different malignant components of a dual tumor, as well as a preponderance of one element over the other. Actually, the neoplasm described consists of two well-defined individual malignant tissues. Inasmuch as the pathogenesis of such a growth is unknown, little is to be gained by speculation as to the relative time factors in the development of each component. Therefore, for the purpose of clarity, it is suggested that the neoplasm be called a mixed sarcoma and adenocarcinoma. The word "mixed" is an important qualifying descriptive factor designed to differentiate the tumor from a situation where sarcomatous and carcinomatous growths exist as separate, independent neoplasms in the same breast.

Concerning the patient's age, the development of a dual mammary neoplasm at 10 years is extraordinary. Only four authentic cases of carcinoma of the breast have been reported as occurring before puberty. The ages were 11 years (Thompson<sup>46</sup>), 11 years (Eliot<sup>46</sup>), 12 years (Levings<sup>47</sup>), and 10 years (Sears and Schlesinger<sup>48</sup>). It is believed that this report constitutes the only recorded instance of a combined sarcoma and carcinoma of the breast of a child.

The method of treatment employed in this case is open to question. While removal of the breast was considered necessary, it was the impression of several examiners who saw the patient before operation that the lesion was benign, most probably mammary hyperplasia of an extreme degree. Accordingly, a simple mastectomy was done without frozen section study. The latter procedure is of established value and it should be employed in all questionable neoplasms of the breast coming to operation. However, the histologic nature of the tumor was such that frozen section would have demonstrated no more than the sarcomatous element. In general, mammary sarcomas rarely invade axillary lymph nodes so that axillary dissection is generally considered illogical in the operative treatment of this lesion, removal of the breast and pectoral muscles being the procedure of choice. This being true, the actual surgical management of the case conformed to the general principles of treatment of sarcoma of the breast, with the exception of removing the pectoral muscles.

Discovery of the carcinomatous factor was made only after sections of the axillary lymphoid tissue were examined. The involved lymph node was excised only because of its proximity to the incision, no attempt being made to dissect the axillary contents. Such being the case, the question arose as to the advisability of a second operation for removal of the pectoral muscles and the lymphoid structures of the axilla and supraclavicular space, after discovering the metastatic carcinoma. Probably such a radical procedure should have been carried out, but factors beyond control prevented it. In spite of the patient's relatively long survival, criticism of the conservative treatment employed is justifiable.

Regarding the uneventful postoperative course, now of three years and ten months' duration, one can only speculate upon the explanation. Several possibilities present themselves. It is quite likely that the entire sarcoma was removed, inasmuch as it appeared to be securely encapsulated. It is conceivable that the carcinoma, which was judged to be early by microscopic study, had metastasized to only a single axillary node, which happened by pure chance to be the one removed. It is probable that postoperative deep x-ray therapy played a responsible part in maintaining the patient's health by holding in abeyance any remaining malignant elements, and that the conservative method of treatment employed makes a permanent cure unlikely.

## SUMMARY

1. A brief discussion of mixed carcinoma and sarcoma of the breast is presented from both clinical and experimental viewpoints.
2. A review of reported cases is prepared in tabulated form.
3. An unusual case of mixed sarcoma and adenocarcinoma in a 10-year-old Negro girl is reported in detail, believed to be the first of its kind recorded in a child.
4. Discussion of the case from three standpoints is included: (1) the nature of the tumor, (2) the patient's age, and (3) the method of treatment regarding prognosis.

Due appreciation is hereby expressed to Dr. H. R. Pratt-Thomas, of the Department of Pathology, for his invaluable help in the preparation of this report.

## REFERENCES

1. Wells, H. G.: Multiple Primary Malignant Tumors: Report of a Primary Sarco-Carcinoma in the Thyroid of a Dog, With mixed Sarcomatous and Carcinomatous Metastases, *J. Path. & Bact.* 7: 357, 1901.
2. Loeb, Leo: Mixed Tumors of the Thyroid Gland, *Am. J. M. Sc.* 125: 243, 1903.
3. Major, R. H.: Multiple Primary Malignant Tumors With Report of a Case of Carcinoma and Sarcoma in the Same Individual, *Bull. Johns Hopkins Hosp.* 29: 223, 1918.
4. Burke, M.: Multiple Primary Cancers, *Am. J. Cancer* 27: 316, 1936.
5. Hurt, H. H., and Broders, A. C.: Multiple Malignant Neoplasms, *J. Lab. & Clin. Med.* 18: 756, 1933.
6. Wehrlein, H. L., and Weber, J. J.: Multiple Primary Malignant Lesions, *Am. J. Surg.* 61: 143, 1943.
7. Kettle, E. H.: Carcinoma and Sarcoma of the Same Breast, *Lancet* 2: 750, 1912.
8. Culphey, W. C.: Primary Spindle-Cell Sarcoma Associated With a Primary Scirrhus Carcinoma, *J. Kansas M. Soc.* 36: 412, 1935.
9. Schwarz, Emil: Carcinoma and Sarcoma Mammae, *Am. J. Obst.* 68: 752, 1913.
10. Lester, C. W.: Sarcoma Associated With Metastases From Breast Carcinoma, *Am. J. Cancer* 15: 850, 1931.
11. Ehrlich, P., and Apolant, H.: Beobachtungen über maligne Mäusetumoren, *Berl. Klin. Wchnschr.* 2: 871, 1905.
12. Haaland, M.: Contributions to the Study of the Development of Sarcoma Under Experimental Conditions, Third Scientific Report of the Investigations of the Imperial Cancer Research Fund, 1908, p. 175.
13. Russell, B. R. G.: Sarcoma Development During the Propagation of a Hemorrhagic Adenocarcinoma of the Mamma of the Mouse, *J. Path. & Bacteriol.* 14: 344, 1910.
14. Nicholson, G. W.: A Small Carcinoma in Association With a Transplanted Sarcoma in a Rat, *J. Path. & Bacteriol.* 16: 518, 1911-12.
15. Harrington, S. W., and Miller, J. M.: A Mixed Tumor (Carcinosarcoma) of the Breast, *SURGERY* 7: 122, 1940.
16. Bouchut, L., and Martin, J. F.: A propos d'un cas de tumeur complexe du sein, *Lyon chirurg.* 18: 425, 1921.
17. Lecène, P.: Tumeur mixte du sein chez la femme (sarcome à myélopaxes et épithéliome pavimenteux), *Bull. et mém. Soc. anat. de Paris* 79: 698, 1904.
18. De Boucaud, and Pierre-Nadal: Tumeur mixte du sein à formations malpighiennes, *Bull. de l'Ass. franç. p. l'étude du cancer* 4: 46, 1911.
19. Cornil, V.: Les tumeurs du sein, Paris, 1903, Baillière et cie.
20. Dorsch: Ueber Karzinom und Sarkom derselben Mamma, Inaugural Dissertation, Wurzburg, 1896. Quoted by Kückens.<sup>42</sup>
21. Kerberiou, and Danel: Sarco-épithéliome kystique de sein, *J. d. sc. méd. de Lille* 1: 175, 1897.
22. Gould, P.: Carcinoma and Sarcoma of the Same Breast. The Middlesex Hospital Reports for the Year 1900, p. 81.

23. Schlagenhauser: Carcinom und Reiszellsarkom derselben Mamma, *Centralbl. f. allg. Path. u. path. Anat.* 17: 385, 1906.
24. Krompecher, E.: Ueber die Beziehungen zwischen Epithel und Bindegewebe bei den Mischgeschwülsten der Haut und der Speicheldrüsen und über das Entstehen der Karcinosarkome, *Beitr. z. path. Anat. u. z. allg. Path.* 44: 88, 1908.
25. Orth, J.: Bericht über das Leichenhaus des Charité-Krankenhauses für das Jahr 1909, *Charité-Ann.*, Berlin 34: 357, 1910.
26. Pfeiffer, D. B.: Mixed Tumor of the Breast, With Malignant Changes Both in the Connective Tissue and Epithelium, *Proc. Path. Soc. Phila.* 13: 267, 1910.
27. Coenen, H.: Ueber Mutationsgeschwülste und ihre Stellung in onkologischen System, *Beitr. z. klin. Chir.* 68: 605, 1910.
28. Secousse, M.: Sur un cas de fibro-sarcome kystique de la mammelle s'accompagnant de points carcinomateux et à contenu gélatineux, *J. de méd. de Bordeaux* 42: 791, 1912.
29. Perrier, H.: Les sarco-carcinomes de sein, *Rev. méd. de la Suisse Rom.* 32: 447, 1912.
30. Waelle: Carcinoms Sarcomatodes der Mamma, Inaugural Dissertation, Zurich, 1913. Quoted by Kückens.<sup>42</sup>
31. Takano, N.: Ueber das Carcinoma Sarcomatodes der Mamma, *Arch. f. klin. Chir.* 103: 155, 1914.
32. Wehner, E.: Ein Beitrag zur Frage der Karcino-sarkom unter Mitteilung eines Mammatumors, *Frankfurt. Ztschr. f. Pathol.*, Wiesb. 16: 167, 1915.
33. Kennedy, J. W., and Case, E. A.: Sarcoma and Carcinoma of the Same Mammary Gland, *Proc. Path. Soc. Phila.* 18: 40, 1915.
34. Hedrén, G.: Sarkocarcinom der Mamma, *Zentralbl. f. allg. Pathol. u. path. Anat.* 26: 265, 1915.
35. Harbitz, F.: Über das gleichzeitige Auftreten mehrerer selbständig wachsender ("multipler") Geschwülste, *Beitr. z. path. Anat. u. z. allg. Path.* 62: 503, 1916.
36. Wilensky, A. O.: A Case of Carcinosarcoma of the Breast, *Proc. N. York Path. Soc.* 19: 113, 1919.
37. Kunsmüller: Ein Karzinomsarcom der Mamma, Inaugural Dissertation, Breslau, 1920. Quoted by Kückens.<sup>42</sup>
38. Jessup, D. S. D.: Giant Cell Sarcoma and Carcinoma in the Same Breast, *Proc. N. York Path. Soc.* 23: 21, 1923.
39. Kreibitz, W.: Zur Kenntnis seltener Geschwulstformen der weiblichen Brustdrüse, *Virchows Arch. f. path. Anat.* 256: 649, 1925.
40. Biebl, M.: Das Mammasarkom und seine Beziehungen zur Fibrosis Mammæ wie zu den gutartigen Mammageschwülsten, *Beitr. z. klin. Chir.* 140: 52, 1927.
41. Helwig, F. C.: Carcinoma of the Breast Combined With a Giant Cell Sarcoma, *Arch. Path. & Lab. Med.* 4: 162, 1927.
42. Kückens, H.: Ueber seltenere Formen von Mammageschwülsten, *Beitr. z. path. Anat. u. z. allg. Path.*, Jena 80: 116, 1928.
43. Pasternack, J. G., and Wirth, J. E.: Adeno-acanthoma Sarcomatodes of the Mammary Gland; Report of a Case With a Critical Review of the Literature of Squamous Epithelium in Intramammary Tumors, *Am. J. Path.* 12: 423, 1936.
44. Mondor, H., Gauthier-Villars, P., and Gottesmann, H.: Carcinosarcome du sein, *Ann. d'anat. path.* 13: 783, 1936.
45. Thompson: Quoted by Deaver, J. B., and McFarland, J.: *The Breast; Its Anomalies, Its Diseases, and Their Treatment*, Philadelphia, 1917, The Blakiston Company, p. 514.
46. Eliot, E.: Breast Cancer in Young Women, *Ann. Surg.* 53: 726, 1911.
47. Levings, A. H.: Carcinoma of the Mammary Gland in a Girl 12 Years Old, *Am. J. Surg.* 31: 29, 1917.
48. Sears, J. B., and Schlesinger, M. J.: Carcinoma of the Breast in a 10 Year Old Girl, *New England J. Med.* 223: 760, 1940.

## BOECK'S SARCOID

### REPORT OF A CASE INVOLVING THE STOMACH

MAJOR IRA GORE, AND LIEUTENANT COLONEL ALPHONSUS M. MCCARTHY,  
MEDICAL CORPS, ARMY OF THE UNITED STATES

PRIOR to 1936, despite a not inconsiderable discussion in the foreign literature, Boeck's sarcoid was a relatively unknown subject to American medicine. Since that time several reviews<sup>2, 3, 6, 8</sup> have brought the condition to the attention of the internist. The surgeon's only contact with it was to provide the biopsy by which the diagnosis is established. Although the disease is not a common one, over a four-year period twenty-three new cases were recognized in a clinic which had become acutely aware of its manifestations.<sup>2</sup> Previously, this condition has not been regarded as surgically important. For this reason it is deemed appropriate to present a brief review and to report a case demonstrating that important surgical complications may develop.

Boeck's sarcoid has come to be regarded as a relatively benign disease of obscure etiology having a predilection for lymphoid tissue<sup>1</sup> but capable of involving any tissue in the body.<sup>2</sup> Despite this potentiality a large proportion of the cases reported are characterized by skin lesions, regional or generalized lymph node enlargement, a stringy or miliary infiltration of the lungs, and cystic changes in the long bones of the hands and feet. In each of these structures the pathologic unit identifying the process is the "hard tubercle" formed of a nodular aggregation of plump polygonal, acidophilic epithelioid cells identical with those found in tuberculosis. Differentiating it from the latter are the almost total absence of caseation, the scarcity of surrounding inflammatory reaction, the absence of demonstrable organisms, and the relative scarcity of Langhans' giant cells. Regarding the latter, the occasional presence of deeply basophilic laminated inclusions in the giant cells is regarded as almost pathognomonic.<sup>1, 2</sup> Guinea pig inoculations of such tissue produce no characteristic reaction. In 60 to 70 per cent of cases there is a negative or very weak tuberculin skin reaction. In the skin, these sarcoid lesions produce sharply defined nodular or papular lesions of variable size, frequently of reddish color involving the skin of the face, extremities, or both. It is of historical interest that this condition was first described as a dermatologic entity.<sup>3</sup> Although Hutchinson in 1875, Besnier in 1889, and Tenneson in 1892 described undoubted instances of the disease, it was not established as a clear-cut entity until Boeck, in 1899, described the pathologic alterations in the skin. Although Boeck<sup>4</sup> noted enlargement of the cubital, femoral, and axillary nodes in his original case and subsequently described involvement of the



deformity of the pyloric antrum through which only very shallow peristaltic waves traveled; this rigidity suggested an intramural infiltration of some kind, probably neoplastic in nature (Fig. 1). There was no evidence of ulceration or of four-hour gastric retention. Stools were negative for occult blood. January 15, 23, and 25, three successive positive Wassermann and Kahn serologic reactions were reported and syphilis of the stomach was considered even though the radiologic findings were not suggestive of this disease. (Quantitative Kahn tests showed an increasing titer from less than 10 units on January 15, to 10 units on January 23, and 40 units on February 8.) Jan. 27, 1943, antisyphilitic treatment was instituted as a therapeutic test. Three doses of neoarsphenamine, one of bismuth, and one of mapharsen were given prior to Feb. 10, 1943. On this date the radiologic appearance of



Fig. 1.—Preoperative x-ray picture illustrating the deformity of the stomach antrum.

the stomach showed persistent, "possibly increased" stenosis of the pyloric antrum of the stomach. Gastric analyses showed an absence of free hydrochloric acid after histamine, total acidity only reaching a maximum of 20 units. Other laboratory findings were essentially negative. The lungs were clear to x-ray. Because of failure to respond to antisyphilitic therapy, the impression at this time was that the patient had a gastric neoplasm, and he was transferred to the surgical service for exploratory laparotomy. The latter was performed, Feb. 23, 1943. Up to this date the patient had received a total of four doses of neoarsphenamine, three of mapharsen, and three of bismuth.

*Operative Findings.*—Laparotomy revealed a diffuse doughy thickening of the pyloric stomach. Both the anterior and posterior walls were involved as well as

the greater curvature. The lymph nodes along the omental attachment were markedly enlarged; the other viscera appeared normal. Biopsies of the thickened stomach wall and of an enlarged lymph node were taken for frozen section. These revealed the inflammatory nature of the lesion, a provisional diagnosis of gastric tuberculosis or sarcoid disease being made; a gastric resection was performed with Balfour-Polya type of anterior loop anastomosis. Postoperative convalescence was uncomplicated. Tuberculin tests with purified protein derivative were negative



Fig. 2.—The mucosal aspect of the surgically excised portion of the stomach. The specimen has been opened along the lesser curvature; the greater curvature lies transversely straddled by a shallow crescentic ulcer. The proximal portion lies to the right, while the pyloric extremity lies to the left.

to the second strength. X-ray pictures showed no bony changes in the metacarpals or metatarsals and an inguinal lymph node presented only inflammatory hyperplasia. April 28, 1943, x-ray studies revealed an adequately functioning gastrojejunal anastomosis. Frequent feedings were necessary because of the small gastric capacity; he slowly gained weight. Intensive antisiphilitic treatment was continued and subsequent to May 27, 1943, the serology on four occasions was negative. June 3, gastric analysis showed an absence of free HCl.

*Pathologic Report*—(S 254 13, A. M. M. Acc. 90296.)

**Gross**—The specimen consisted of a large segment of the gastric antrum measuring 8 cm. along the lesser curvature and 12 cm. along the greater curvature. On the anterior surface about 8 cm. proximal to the pyloric extremity there was a 4 cm., recently sutured linear incision covered with a small omental tag; this apparently was the seat of the biopsy. The serosal surface was shiny and translucent. However, toward the attachment of the omentum numbers of tiny slightly elevated translucent nodules were evident. Palpation revealed extensive thickening and induration of a rather large area on the greater curvature at about the mid portion of the specimen. The specimen was opened along the lesser curvature (Fig. 2).



Fig. 3.—Photomicrograph through the stomach wall illustrating the marked thickening the shallow mucosal ulceration prominent endarteritic changes and small pale nodules just below the mucosa to the left of the ulcer ( $\times 10$  U. S. Army Medical Museum).

On the mucosal surface straddling the greater curvature 8 cm. proximal to the pyloric end, there was a crescentic, moderately deep ulceration. It measured 5 cm. in length and varied in width from 1 to 2 cm. The biopsy described externally evidently included the anterior pole of the ulcer, since in the operative specimen this part was markedly narrowed by the repairing suture. Proximal to the ulcer the mucosal folds were thickened and formed a sharply angulated overhanging wall. There was a slight tendency for puckering of the folds in the direction of the ulcer. The distal margin of the ulcer was comparatively poorly defined. Section of the stomach wall showed marked scarring and thickening of the submucosal layer underlying the ulcer site and extending toward the pylorus. At places along this line the gastric wall measured 2 cm. in thickness. The muscularis was intact and hyperplastic (Fig. 3).

Accompanying the specimen was a moderately enlarged lymph node removed from the omentum. The node measured 1 by 2 by 1.5 cm. and its capsule was thin and intact. Section revealed a yellowish pink homogeneous surface.

**Microscopic** (Figs. 3 and 4).—Sections taken from the pyloric portion of the stomach showed an extensive round and plasma cell infiltration of the mucosa. The glandular epithelium showed variable cystic changes. There was moderate atrophy toward the pylorus where small pits were present.

The ulceration noted grossly barely penetrated the muscularis mucosae. A small quantity of purulent exudate was noted on its surface. The ulcer bed consisted of a rather thin layer of chronically inflamed granulation tissue. The underlying submucosa was markedly edematous and moderately scarred. The submucosal vessels showed rather marked endarteritic changes. Heavy mantles of round and plasma cells accompanied the vessels. In the mucosa and superficial submucosa adjacent to the ulcer there were nodular aggregates of epithelioid cells. These were unassociated with caseation or necrosis, and giant cells were rare. The muscularis was thickened by scar tissue and round-cell infiltration. The serosal surface contained a number of small lymphoid nodules in the centers of which epithelioid cells and an occasional Langhans' type giant cell were found; concentric laminated basophilic giant cell inclusions were demonstrable.

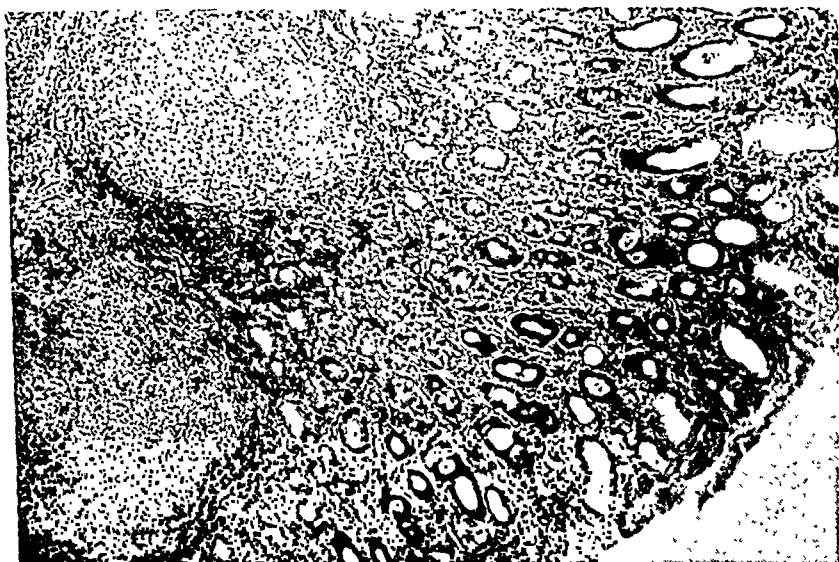


Fig. 4.—Gastric mucosa demonstrating nodular aggregates of epithelioid cells lying, in this instance, just above the muscularis mucosae. Note also the diffuse lymphocytic infiltrate and the glandular changes which signify chronic gastritis. (X100. U. S. Army Medical Museum.)

Sections taken from the lymph node exhibited similar nodular clusters of epithelioid cells. Again there was no necrosis, and giant cells were rare. There was a rather marked tendency toward hyaline scarring. The surrounding nodal parenchyma was hyperplastic and contained large numbers of plasma cells. The sinus endothelium was hyperplastic. Acid-fast bacilli were not demonstrable histologically or in digests and concentrates of portions of the specimen.

*Diagnosis.*—(1) Boeck's sarcoid of the stomach and lymph node and (2) subacute ulceration of the pyloric stomach.

We are aware of only one other case of gastric sarcoid (unpublished), presented by Dr. Fred Stewart to a surgical pathology conference of the New York State Laboratory Association in November, 1942.

#### DISCUSSION

As has been intimated, the preoperative diagnoses considered were peptic ulcer, gastric syphilis, and gastric neoplasm. Ulceration was understandably not demonstrated by x-ray since the ulcer was shallow and its position on the greater curvature did not lend itself to easy

demonstration. Furthermore, the presence of achlorhydria, the position of the lesion, and the lack of melena appeared to corroborate the negative roentgenologic findings. Peptic ulceration was therefore considered unlikely.

Gastric syphilis was considered a likely possibility because of a rising serologic titer, the relative youth of the patient, and the position of the lesion in the distal portion of the stomach.<sup>14, 15</sup> However, gastric syphilis is considered to be a manifestation of the tertiary phase of the disease, and in this case, although a history of a primary lesion is absent the change in serologic reaction from negative to positive, the consistent rise in serologic titer associated therewith, and the relatively prompt return to seronegativity under arsenotherapy all would indicate this to be certainly not late syphilis. Nonetheless, it was considered advisable to institute a therapeutic test of antisyphilitic treatment. There was no response to a short intensive course and after four weeks laparotomy was performed, the presumptive diagnosis being gastric neoplasm.

At operation, frozen sections ruled out a neoplastic process but resection was considered advisable since the lesion appeared to be progressing clinically. As the microphotographs (Figs. 3 and 4) demonstrate, the distinctive lesions of sarcoid are present in addition to secondary ulceration and rather extensive nonspecific productive inflammatory response. The prominence of the endarteritic changes and of the perivascular cellular infiltrate is suggestive of a syphilitic lesion but these processes are also commonly present in nonspecific ulceration. Endophlebitis, whose diagnostic value in syphilis has been demonstrated by Williams and Kimmelstiel,<sup>15</sup> could not be shown. Supported by the clinical features and course already described, the microscopic picture was considered not to represent syphilis.

From the first, one of the striking diagnostic features of Boeck's sarcoid was the comparative lack of surrounding inflammation. However, the mere mechanical presence of the sarcoid nodules in a mucosal surface subject to repeated physiologic trauma is felt sufficient to invoke an inflammatory response as in this case. Presumably, ulceration occurred secondarily, an impression substantiated by Hebbel's<sup>16</sup> work on chronic gastritis and ulceration.

It is not possible to draw any conclusions as to treatment from one case of "surgical" sarcoid disease. Each case must be individualized. Although there is a strong tendency toward spontaneous resolution in the primary disease, it is the secondary complication making the case "surgical" that must be gauged in treating the patient.

#### REFERENCES

1. Schaumann, J.: Benign Lymphogranuloma and Its Cutaneous Manifestations, *Brit. J. Dermat.* 36: 515, 1924.  
Idem: Lymphogranulomatosis Benigna in the Light of Prolonged Clinical Observations and Autopsy Findings, *Brit. J. Dermat.* 48: 399, 1936.

- Idem: On the Nature of Certain Peculiar Corpuseles Present in the Tissue of Lymphogranuloma Benign, *Acta. med. Scandinav.* 106: 239, 1941.
2. Longcope, W. T.: Sarcoidosis or Besnier Boeck-Schaumann Disease, *J. A. M. A.* 117: 1321, 1941.
  3. Hunter, F. T.: Hutchinson-Boeck's Disease, *New England J. Med.* 214: 346, 1936.
  4. Boeck, C.: Multiple Benign Sarcoid of Skin, *J. Cutan. & Genito-Urin. Dis.* 17: 543, 1899.
  5. Jungling, O.: Ueber ostitis tuberculosa multiplex cystoides, *Beitr. z. klin. Chir.* 143: 401, 1928.
  6. Longcope, W. T., and Pierson, J. W.: Boeck's Sarcoid, *Bull. Johns Hopkins Hosp.* 60: 223, 1937.
  7. Nickerson, S. A.: Boeck's Sarcoid: Report of Six Autopsied Cases, *Arch. Path.* 24: 19, 1937.
  8. Pinner, M.: Noncaseating Tuberculosis, *Am. Rev. Tuberc.* 37: 690, 1938.
  9. Longcope, W. T., and Fisher, A. M.: Involvement of the Heart in Sarcoidosis, *J. Mt. Sinai Hosp.* 8: 784, 1942.
  10. Tillgren, J.: Diabetes Insipidus as a Symptom of Schaumann's Disease, *Brit. J. Dermat.* 47: 223, 1935.
  11. Rakov, H. L., and Taylor, J. S.: Sarcoidosis, *J. Lab. & Clin. Med.* 27: 1284, 1942.
  12. Lenartowicz, J., and Rothfeld, J.: Ein Fall von Hautsarkoiden mit identischen Veränderungen im Gehirn und den inneren Organen, *Arch. f. Dermat. u. Syph.* 161: 504, 1930.
  13. Bernstein, M., Konzlemann, F. W., and Sidlick, D. M.: Boeck's Sarcoid; Report of a Case with Visceral Involvement, *Arch. Int. Med.* 44: 721, 1929.
  14. Palmer, W. L., Schindler, R., Templeton, R. E., and Humphreys, E. M.: Syphilis of The Stomach; Case Report, *Ann. Int. Med.* 18: 393, 1943.
  15. Williams, C., and Kimmelstiel, P.: Syphilis of the Stomach, *J. A. M. A.* 115: 578, 1940.
  16. Hebbel, R.: Chronic Gastritis: Its Relation to Gastric and Duodenal Ulcer and to Gastric Carcinoma, *Am. J. Path.* 19: 43, 1943.

## COMPOUND CRANIOCEREBRAL INJURIES

WILLIAM J. GERMAN, M.D., BERNARD S. BRODY, M.D., AND  
SAMUEL C. HARVEY, M.D., NEW HAVEN, CONN.

*(From the Department of Surgery, Yale University School of Medicine)*

THE present shortage of specialists in many communities necessitates that the general surgeon again become a general surgeon in fact as well as in name. This applies to the field of neurosurgery, where a high percentage of those certified in this specialty are now serving with the Armed Forces. Within the Services, certain neurosurgical procedures must likewise be carried out by general surgeons, due to the necessary distribution of neurosurgeons over a vast geographical area. In both civilian and service practice the problems of trauma to the nervous system frequently require the attention of the general surgeon. Of these problems, compound craniocerebral injury is the subject which most often requires urgent, definitive, rational treatment. The present report is based upon the methods of treatment and the results obtained in patients with compound craniocerebral injuries admitted to the New Haven Hospital over a period of fourteen years.

Prior to World War I there was no unanimity of opinion concerning the treatment of compound craniocerebral wounds. During the early years of that war, operations for these wounds acquired bad repute from the high incidence of infection and death. Even scalp wounds were subject to frequent infection. Cushing's critical analysis of this situation was crystallized in his statement that the poor results were "largely due to delay—delay in transit, which may be avoidable; unnecessary delay after admission, which often is avoidable." In addition to his emphasis upon early treatment, Cushing<sup>1</sup> made an outstanding contribution by devising and applying methods of treatment in which "the same principles of débridement utilized so successfully for wounds elsewhere have in their essentials been adapted to wounds involving the brain." His results with débridement en bloc were presented in one of the finest surgical contributions that ever emerged from the smoke of battle.<sup>1</sup>

After World War I these principles were applied to the treatment of civilian injuries. In 1923 Harvey<sup>2</sup> reported on a group of 154 patients with skull fracture treated in the New Haven Hospital between 1919 and 1923. In this series the dura was penetrated in 14 patients (9 per cent); of these, 4 died, a mortality of 28 per cent. Of the 9 operated upon, 1

Presented in part at the meeting of the Society of University Surgeons, Nashville, Tenn., Feb. 10-12, 1944.

Received for publication, April 23, 1944.

TABLE I  
HEAD INJURIES ACCORDING TO SEVERITY  
(CUSHING, 1918)

	MORTALITY (%)
Scalp, intact cranium and dura	4.5
Local fracture, dura intact	9.2
Depressed fracture, dura punctured	11.8
Fracture, bone fragments in brain	24.0
Bone and projectile in brain	36.6
Penetrating ventricles, bone	42.8
Penetrating ventricles, projectile	100.0
Craniocerebral, air sinuses	73.0
Craniocerebral, traversing	80.0
Craniocerebral, with massive fracture	50.0

died on the table with a traversing wound and extensive intracranial hemorrhage. There were no deaths from infection. Harvey stated, "From experience gained during the late war it is known that wounds thoroughly débrided and sutured in the first six hours heal per primam in something over 90 per cent, while the delay of twelve hours adds not more than 10 per cent to the number that will break down. It takes, then, in most instances, from six to twelve hours for the infective agent to establish itself in the tissues in such a manner that it cannot be eradicated by thorough débridement."

Later, for reasons which are difficult to evaluate, there appeared in some localities a tendency to delay operative treatment. Munro,<sup>3</sup> in 1938, advocated a delay of twenty-four hours in all instances but advised against operation after forty-eight hours. In Munro's series of 136 operable injuries the mortality was 30.8 per cent, and the morbidity, chiefly due to infection, was stated to have been about 24 per cent, although all but 5.5 per cent were thought to be attributable to technical errors. In 1943 Munro<sup>4</sup> reported on study of 218 patients with compound fracture of the skull; 159 (73 per cent) were considered operable. The incidence of compound fractures of the skull in the entire group of patients with head injuries treated by Munro was 11.3 per cent. The operative mortality was 15.7 per cent. The incidence of infection in the patients operated on was 24.5 per cent. Munro considered as septic all wounds that did not heal by first intention; in case drains were inserted, the union of the wound, exclusive of the drainage tract, was used as the measure of the type of healing. In this series he eliminated the period of delay except in those cases in which the patient's condition was not satisfactory. Munro further advised that the operation be done before forty-eight hours after the receipt of the injury or else postponed for from six to eight months.

At the beginning of World War II the British<sup>5</sup> recognized the advisability of providing for early treatment of compound cranioerebral injuries by specially equipped and trained teams. Mobile neurosurgical units were utilized, but in France they were captured before their worth



had been tested. A similar attempt was made in the Middle East, but owing to the difficulty of segregating casualties in the forward areas, only 10 per cent of those reaching the neurosurgical unit had head injuries. It was therefore decided to base the unit behind the general hospital. This meant a delay in primary operation of approximately forty-eight hours. Working under these conditions, Ascroft<sup>6</sup> reported a series of 516 wounds (Table II) due to missiles; 292 were associated with penetration of the dura. The wounds received preliminary cleansing, sulfonamide powder was used and sulfadiazine was given by mouth or intravenously after operation. The mortality rate was excellent: 1.5 per cent in those with intact dura; 15 per cent with dural penetration. But a disquieting feature was that about 1 of 4 (75 out of 292) patients with penetrating wounds developed brain abscess. There were 17 deaths due to brain abscess. About 40 per cent of all deaths in Ascroft's series were due to abscess, and abscess played a part, often decisive, in rendering unfit for military service 40 per cent of all men incapacitated by penetrating wounds of the brain.

With the break-through at El Alamein, the lines of communication became so long that Eden,<sup>7</sup> who was then in charge, moved forward. His series of 293 patients (Table II) included 102 with compound cranial injuries with penetration of the dura and most of them were operated upon within twenty-four hours of injury, although in a few the wounds were more than three days old. Most of the patients reaching Eden had had no treatment other than a dressing of sulfanilamide powder to the wound and sulfanilamide orally or sulfadiazine intravenously. The incidence of intracranial infection in 102 patients with dural penetration was as follows: meningitis, 5; cerebral abscess, 1. As a result of getting patients with such wounds for early treatment the lowered incidence of infection is well reflected in the fall of serious complications as compared with Ascroft's results. The postoperative mortality in the 102 patients with dural penetration was 23.6 per cent (Eden). Primary healing of the wounds was obtained in over 90 per cent of the patients operated upon within the first forty-eight hours. Table II gives a compilation of Ascroft's and Eden's results.

TABLE II  
COMPARATIVE MORTALITY FIGURES IN THE ASCROFT AND EDEN SERIES

	NUMBER OF PATIENTS		MORTALITY			
			ALL CAUSES (%)		FROM INFECTION (%)	
	ASCROFT	EDEN	ASCROFT	EDEN	ASCROFT	EDEN
Scalp wound	85	139	0	0	0	0
Fracture skull (dura intact)	139	69	1.5	1.4	0	0
Fracture skull (dura penetrated)	292	102	15.0	23.6	8.5	5.0
Total	516	310	9.0	8.6	4.8	1.6

Another striking example of the advantage of early operation is the report of Cloward<sup>5</sup> on a group of cranial injuries arising from the Pearl Harbor attack (he was not permitted to report the number of persons treated). Nearly all of the wounds were compound depressed fractures of the skull produced by fragments of shrapnel. His policy was to operate as soon as possible, but because of the large number of patients treated, it was necessary in many instances to delay as long as from twenty-four to thirty-six hours. No infection was encountered in any of the patients in whom a preliminary cleansing of the wound was carried out and sulfonamide powder used locally. It is unfortunate that Cloward's excellent results were attributed, by many, entirely to the effectiveness of sulfonamide therapy and the factor of early, skillful operation under favorable circumstances was overlooked.

The present series consists of 64 patients with compound craniocerebral injuries treated at the New Haven Hospital from 1928 to 1942. Basilar fractures through the air sinuses without exposure of the dura or brain were not included. Four patients died within one and one-half hours after admission to the hospital before preparations for operation were completed. The remaining 60 patients were operated upon. The operators included five members of the senior staff and the neurosurgical residents. The general policy in treatment was as follows: (1) immediate treatment of shock if present; (2) inspection and *not* palpation of the wound; (3) x-ray for extent of fracture, especially for depression and sinus involvement; (4) operation within six hours in *all* patients surviving the preparatory period (usually two hours). Local novocain was the anesthetic of choice. The essentials in the surgical procedure were (1) thorough débridement of the scalp, cranial wound, and devitalized brain tissue; (2) removal of indriven bone fragments and foreign bodies; (3) closure of the dura (silk) if possible; (4) closure of the scalp in two layers (silk); (5) drainage of the frontal sinuses and of most wounds for culture. The bone removal was usually en bloc for the comminuted and depressed fractures, unless the frontal or sagittal sinuses were involved, in which case fragments were removed. In the case of linear fractures, the fissures were cleaned, but no bone was removed.

The distribution of patients according to age is shown in Table III. About 60 per cent of the patients were in the first three decades, but a significant number (14 per cent) were over 60 years of age. It is noteworthy that all of these patients in the seventh and eighth decades died;

TABLE III  
DISTRIBUTION AS TO AGE (64 CASES)

	DECADE							
	1	2	3	4	5	6	7	8
Number of cases	11	11	16	7	7	3	7	2
Deaths	3	1	1	2	0	1	7	2

53 per cent of the total mortality (9 of the 17 deaths) occurred in this group.

The sex incidence followed roughly a ratio of 4 to 1 in favor of the males. The injury was due to a missile in 9 patients. The remaining 55 were injured as follows: Automobile accident, 42; accidental fall, 5; struck by blunt object, 8.

Associated injuries were present in 33 patients, being minor in 11 and major in 22. Fractures of the facial bones, ribs, and long bones accounted for 19 of the major injuries; laceration of the liver was noted in 1. The minor injuries consisted of contusions and lacerations.

*Period of Unconsciousness.*—There were 15 patients who gave no history of loss of consciousness, although it is possible that in some of these at least a transient break in the stream of consciousness may have escaped recognition. Twenty-three patients were semiconscious or unconscious for less than one hour, 18 from one to ten hours, and 8 for more than twenty-four hours. Thirteen patients died without regaining consciousness. Coma is generally recognized as a grave prognostic sign. Table IV shows the postoperative mortality classified in terms of the degree of consciousness on arrival at the hospital.

TABLE IV  
MORTALITY RELATED TO STATE OF CONSCIOUSNESS

	COMA	SEMICONSCIOUS	ALERT
Number dying	16	0	1*
Number surviving	9	7	31

\*See text.

The single fatality in the alert group\* was a patient 65 years of age who died of a cerebral hemorrhage on the third day following the injury (bullet). One patient in coma on arrival died of a complicating infection. It is notable that more than one-third of the patients arriving in deep coma survived. It does not seem warranted therefore to leave these patients for some hours the better to assess their chances while at the same time increasing the possibilities of infection by delay. However, where large numbers of battle casualties require urgent treatment, the state of consciousness is an important factor in selecting the more favorable cases for early operation (Eden<sup>7</sup>).

*Shock.*—The records were adequate for the determination of the presence of shock in 59 of the 64 patients. On the basis of a systolic blood pressure below 100 on admission or at the beginning of the operation, shock was present in 15. Seven of these patients died; of these, 2 died before preparations for operation had been completed. An analysis of the remaining 5 deaths shows the time and cause as follows: (1) Four and one-half hours, extensive brain damage and compound fractures of

\*See Table IV.

both legs (operation consisted only of closure of scalp wound); (2) six hours, gross laceration of brain with brain tissue extruding; (3) twenty-four hours, extensive subdural hematoma found at post-mortem; (4) seven days, bilateral bronchopneumonia; (5) five weeks, intracranial infection. Four of these patients were over 60 years of age. Moderate shock was present at the beginning of the operation in only 4 of the 60 patients. Shock should rarely delay an operation for more than six hours. With present methods for the treatment of shock it should be possible to correct this condition within six hours except in those with the most severe intracranial injuries and in those with continuous concealed hemorrhage in the abdomen or thorax.

*Operations.*—Four patients died within one and one-half hours after the injury, before preparations for operation were completed. The remaining 60 patients were taken to the operating room as soon as the extent of the injury was determined and appropriate measures for the treatment of shock and associated injuries were completed; the operability rate was 93.8 per cent. Operation was begun within six hours after the injury in all but 2 patients.

TABLE V  
TIME INTERVAL BETWEEN INJURY AND OPERATION

Number of hours	Less than 4	4 to 6	7	9
Number of cases	48	10	1	1

*Types of Operations.*—Bloc removal of the compound scalp and cranial wound was done in 19 of the 52 patients in whom projectiles were not involved. This group included most of the more severely injured. The operative mortality was 26 per cent. Excision of the scalp wound and fragment removal of the cranial wound was done in 20 patients, including those with orbitonasal injuries and many with less severe injuries to the cranial vault. The operative mortality was 10 per cent. Débridement of the scalp wound without bone removal was done in 13 patients. The wounds were chiefly linear fractures with little or no depression. The operative mortality was 7.7 per cent. The total operative mortality for the entire series of 52 patients with nonprojectile injuries was 15.4 per cent. The series of projectile injuries (9, was too small to assess the results in relation to the types of operative procedure employed.

Primary closure of the scalp wound was done in all instances. Drains were inserted in the wounds of 29 of the 60 patients operated on; the drains were usually removed within twenty-four or forty-eight hours. The dura was closed whenever possible; the reasons for leaving the dura open were as follows: pinpoint openings, dural tension, and shredded dura.

*Postoperative Infection.*—Records of patients who died in the first six days following operation were not included in the statistical analysis.

(Table VI), since the time interval was not sufficient to exclude the possibility of infection had the patient survived. In the remaining 51 patients, serious infection was present in 2, and of these, 1 died, a mortality of 2 per cent. Infections confined to the drainage tracts were included as wound infections.

TABLE VI  
POSTOPERATIVE INFECTION (51 PATIENTS LIVING OVER SIX DAYS)

Cerebritis	1	(2%)
Meningitis	1	(2%)
Local osteo.	2*	(4%)
Scalp	7	(14%)
Total	10	(20%)

\*Local osteo. and meningitis in one patient, with nasofrontal injury.

Only 2 scalp infections occurred in patients in whom drainage had not been used. A complete bloc débridement was done in only 1 of the patients developing infections. The débridement in these patients was limited in most instances because the frontal sinus was close to or involved in the fracture.

Munro<sup>9</sup> reported a bacteriologic study of 70 patients with compound fractures of the skull. It appears that the degree of culturable contamination of the wound varies from 55 to 60 per cent during the first forty-eight hours and rises sharply thereafter. Thirty-one wounds were swabbed within twenty-four hours or less of the receipt of the injury. Seventeen (55 per cent) of this group showed pathogenic bacteria (*Staphylococcus aureus* in all but two). Forty-four wounds were forty-eight hours old or less when cultured. Twenty-six grew pathogenic bacteria (pure *Staph. aureus* in 21 of these). The rather high incidence of contaminated wounds within the first twenty-four hours with pathogenic organisms underscores the necessity for early and thorough débridement. Many of the staphylococcal wound infections are endogenous and not exogenous in origin, yet care must be taken *not to introduce contamination* into the wound by unnecessary finger palpation. Brain wounds in battle casualties are seldom sterile. The Russians found only 2 of 300 such wounds to be sterile.

*Mortality.*—It has been said by many writers that mortality figures have little real significance since no two studies are based upon identical clinical material. Eden<sup>7</sup> stated, "The mortality figure has really little meaning, for the mortality in these cases depends to a great extent on how near you are to the front and what you operate on." In the present series, no patient was denied operation because he was considered to be a "poor risk." The operability rate of 93.8 per cent included all patients who survived for over one and one-half hours following injury. The *total mortality* in the entire series of 64 patients was 26.5 per cent, only a trifle higher than Munro's<sup>3</sup> estimate of 24 per cent for the aver-

age mortality of about 120,000 cases of all types of head injuries, most of which were of the closed type. The *operative mortality* in all compound cranioerebral injuries in the present series was 21.6 per cent.

Of the 9 patients in this series with injuries due to missiles, 6 died (1 before operation), a mortality of 66.7 per cent; operative mortality, 62.5 per cent. All 4 of the patients with traversing wounds died following operation. The single fatality resulting from nontraversing missiles (mortality 25 per cent) was due to severe kidney damage and uremia from prophylactic sulfapyridine therapy.

There were 52 patients operated upon for injuries not produced by projectiles, with a *mortality* of 15.4 per cent. One-half of the post-operative deaths occurred in patients over 60 years of age.

TABLE VII

OPERATIVE MORTALITY RELATED TO SEVERITY OF INJURY  
(52 CASES OF COMPOUND FRACTURE—EXCLUSIVE OF INJURIES DUE TO MISSILES)

	CASES	DEATHS
I. Fracture, dura intact	29	2 (7%)
II. Fracture, dura open	6	1 (17%)
III. Fracture, dura open plus laceration or contusion of brain	9	2 (22%)
IV. III plus indriven bone fragments	8	3 (37%)
Total	52	8 (15.4%)

*Cause of Death.*—Autopsies were obtained in 5 of the 17 patients who died. All 5 of these patients had been operated upon. Four patients died before operation. The projectile injuries account for 35.3 per cent of the total deaths.

TABLE VIII

CAUSE OF DEATH—PROJECTILE INJURIES  
(9 CASES, 6 DEATHS)

Extensive brain damage	3*
Massive subdural hemorrhage	1
Renal hemorrhage, uremia, prophylactic sulfapyridine	1
Cerebral hemorrhage, hypertension	1
Total	6

Deaths in missile group (3 over age of 60).

\*No operation in one.

TABLE IX

CAUSE OF DEATH—NONPROJECTILE INJURIES  
(55 CASES, 11 DEATHS)

Extensive brain damage	7*
Contralateral subdural hematoma	1
Infection (cerebritis)	1
Bronchopneumonia	2
Total	11

Deaths in group with nonprojectile injuries (6 over age 60).

\*No operation in three.

*Summary and Conclusions.*—Accumulated experience during World War I indicated that early operation and thorough débridement were of primary importance in the treatment of compound craniocerebral injuries. Cushing was largely responsible for laying down these principles of treatment as an essential basis for controlling infection, which was so largely responsible for the high mortality encountered in the early years of World War I. Later, for reasons difficult to evaluate, there appeared in some localities a tendency to delay operative treatment. At the beginning of World War II the British policy included early treatment of compound craniocerebral injuries, and a comparative study of two series (Ascroft, Eden) indicates a higher incidence of serious infection where operation was unavoidably delayed.

The present report consists of 64 compound craniocerebral injuries treated at the New Haven Hospital from 1928 to 1942, 9 of which were due to missiles. Sixty patients were operated upon; 4 patients died within one and one-half hours after admission to the hospital. No patient was denied operation because he was considered to be a "poor risk." It is notable that more than one-third of the patients arriving in deep coma survived. It does not seem warranted therefore to leave these patients for some hours the better to assess their chances while at the same time increasing the possibility of infection by delay. Operation was begun within six hours in all but 2 patients. Moderate shock was present at the beginning of the operation in only 4. With present methods for the treatment of shock, it should be possible to correct this condition within six hours except in the most severe intracranial injuries and in those patients with continuous bleeding in the abdomen or thorax.

The general policy in treatment was as follows: (1) immediate treatment of shock *if present*; (2) inspection and *not* palpation of the wound; (3) x-ray for extent of fracture, especially for depression and sinus involvement; (4) operation within six hours in *all* patients surviving the preparatory period (usually two hours). Thorough débridement of the scalp, cranial wound, and devitalized brain tissue was stressed. The bone removal was usually en bloc for the comminuted and depressed fractures, unless the frontal or sagittal sinuses were involved, in which instance fragments were removed. Complete excision of the scalp and brain wounds and removal of foreign bodies from the brain were considered essential in averting infection. Serious infection occurred in only 2 patients in this series, 1 of whom died; the mortality from infection was 2 per cent.

The *total mortality* for the entire series of 64 cases was 26.5 per cent, only a trifle higher than Munro's estimate of 24 per cent for the average mortality of about 120,000 cases of all types of head injuries, most of which were of the closed type. The projectile injuries (9 cases) accounted for 35.3 per cent of the total deaths. The *operative mortality* of all compound craniocerebral injuries in this series was 21.6 per cent.

There were 52 patients operated upon for injuries not produced by projectiles, with an *operative mortality* of 15.4 per cent. One-half of the postoperative deaths occurred in patients over 60 years of age.

## REFERENCES

1. Cushing, H.: A Study of a Series of Wounds Involving the Brain and Its Enveloping Structures, *Brit. J. Surg.* 5: 558-684, 1918.
2. Harvey, S. C.: *Compound Cranio-Cerebral Injuries*, Boston, M. & S. J. 189: 911-914, 1923.
3. Munro, D.: *Cranio-Cerebral Injuries: Their Diagnosis and Treatment*, London, New York, 1938, Oxford University Press.
4. Munro, D.: *Compound Fractures of the Skull. The Results of Surgical Therapy in Two Hundred and Eighteen Cases*, *New England J. Med.* 228: 737-745, 1943.
5. Cairns, H., and Guttman, E.: A Review of Recent German Work on Gunshot Wounds of the Head, *Bull. War Med.* 3: 477-484, 1943.
6. Ascroft, P. B.: Treatment of Head Wounds Due to Missiles. Analysis of 500 Cases, *Lancet* 2: 211-218, 1943.
7. Eden, Kenneth: Mobile Neurosurgery in Warfare, *Lancet* 2: 689-692, 1943.
8. Cloward, R. B.: War Injuries to the Head. Treatment of Penetrating Wounds, *J. A. M. A.* 118: 267-270, 1942.
9. Munro, D.: The Bacteriology of the Wounds of Compound Fractures of the Skull, *New England J. Med.* 227: 939-944, 1942.



## IMPROVED RETRACTOR FOR HEMI-LAMINECTOMY\*

LIEUTENANT C. HUNTER SHELDEN, AND LIEUTENANT ROBERT H. PUDENZ  
MEDICAL CORPS, U. S. N. R.

ADEQUATE exposure in the limited operative field is essential for successful removal of protruded intervertebral discs. The average laminectomy retractor was designed to retract both sacrospinalis muscle groups, thus allowing complete removal of the spinous processes and laminae. Hemilaminectomy requires the separation of only one muscle group from the spinous process. This more conservative procedure introduces a new problem of exposure because the mesial margin of the operative field includes the bony spinous process. Fixation of one blade of the usual retractor to the bone is not only difficult but, if successful, occupies valuable space in the already limited field of exposure. If the mesial blade is inserted into the fascia and muscle of the opposite sacrospinalis muscle group, the situation is somewhat improved but still not ideal because the blade in the wound must be placed at a deeper level. Thus, with strong retraction it is difficult

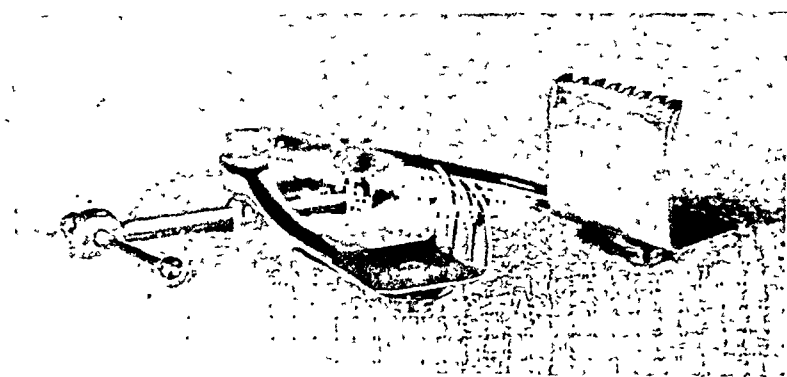


Fig. 1.—Photograph of retractor showing shape of the blades.

to prevent the deeper of the two blades from slipping. This allows the muscle fibers adjacent to the lamina to slide from beneath the retractor. If the blade against the muscle is deep enough to catch all the muscle fibers, there is frequently a rotation of the entire retractor because of the extreme difference in depth of the two blades.

In an attempt to obviate these mechanical difficulties a retractor was designed with blades of unequal length (Fig. 1). The shorter blade has three long teeth which are inserted through the lumbar fascia

\*The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or as reflecting the views of the Navy Department or the Naval Service at large.

Received for publication, May 29, 1944.

adjacent to the spinous processes. The longer blade, which is used for the muscle retraction, is two inches wide, slightly curved, and has small laterally bent serrations on the free end which fix the blade at the desired depth. The ease with which these blades may be produced in any machine shop makes it possible to have several lengths available.

These blades are attached to the arms of a Lilienthal rib spreader which possesses a screw adjustment that allows forceful retraction. The Lilienthal retractor was selected because it possesses removable

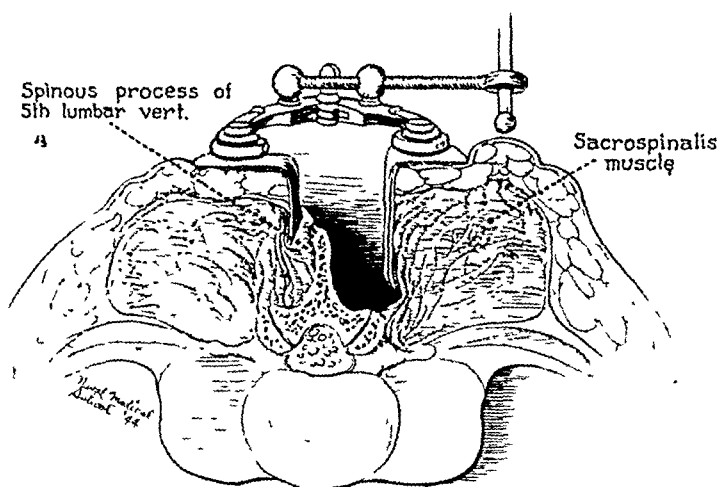


Fig. 2.—Exposure for hemilaminectomy, demonstrating method of muscle retraction.

blades, a distinct advantage when converted into a laminectomy retractor for it allows one to use a blade which corresponds in length to the size of the sacrospinalis muscle group. The exchange of blades is a simple matter and requires but a few seconds.

Hemilaminectomy is simplified and exposure improved particularly in those individuals with strong muscles and poor relaxation (Fig. 2). Although originally designed for lumbar hemilaminectomy, it has proved to be equally adapted for use in the cervical region.

## A LIMITED COMPARISON OF CONTINUOUS SPINAL AND GENERAL ETHER ANESTHESIA

WILLIAM GRANT COOPER, II, M.D., WILMA ZUMWALT, R.N., AND  
EVERETT D. SUGARBAKER, M.D., COLUMBIA, MO.

*(From the Surgical Department of the Ellis Fischel State Cancer Hospital)*

THE relative advantages of spinal and inhalation ether anesthesia have been the subject of much discussion. The primary weakness of spinal anesthesia as heretofore administered, and the one on which many of the objections to its use have depended, has been the uncertainty of and the inability to lengthen its duration. This shortcoming may now be completely eliminated by the use of the continuous principle, so that it seems worth while to attempt a revaluation of the subject. An exceptional opportunity to do this was presented when a particular series of anesthetics were given at this hospital. From January, 1940, to February, 1942, one of us (W. Z.) gave all the general ether anesthetics, and from February, 1942, to September, 1943, gave continuous spinal anesthesia to all patients requiring operation below the diaphragm.

The patients' age groups, their general condition, the primary diagnosis, and procedures carried out under each type of anesthesia were essentially similar. The operations were done by or under the supervision of only two surgeons.

The general anesthetics were administered by the closed system. Nitrous oxide was used for induction and the anesthesia maintained with inhalation ether and oxygen. This method has traditionally been satisfactory. The continuous spinal anesthetics were given by the method of Lemmon with certain modifications, which will be discussed later. No attempt was made to select cases for spinal anesthesia. That is to say, no patient was denied spinal anesthesia because something about his condition raised theoretical objections to its use.

This hospital treats indigent patients suffering from cancer. The average age on admission is about 60 years, and anemia, hypoproteinemia, and the diseases associated with advanced age are commonly seen in association with the tumor for which treatment is sought. Poor general condition is particularly frequent in those subjected to abdominal operation, as most of these are patients with gastrointestinal cancer. Careful attempt is made preoperatively to restore these patients physiologically as nearly as possible to normal. Still they present a severe test of the efficiency and safety of whatever anesthetic method is used.

The material selected for study consists of two series of 100 anesthetics each. The first group comprises the last consecutive 100 general anesthetics given for operations below the diaphragm. The second group consists of the first and the last consecutive 50 continuous spinal anesthetics given by the same anesthetist. As continuous spinal anesthesia is used only for operations below the diaphragm, the two groups are nicely comparable. The first and last 50 cases in which the patients were given continuous spinal anesthesia were considered in order to compare results obtained earlier with those obtained after we had acquired some experience with this method.

The comparative tabulation is presented in Table I.

TABLE I  
INDICATING THE SIMILARITY OF THE TWO GROUPS

	CONTINUOUS SPINAL ANESTHESIA	GENERAL ANESTHESIA
Average age (yr.)	60	55
Per cent with cancer	72	69
Radical intestinal resections	20	21
Other extensive majors	7	8
Inoperable exploratory laparotomies	22	18
Remaining number of cases	51	53
Cases requiring over two hours	50	37
Cases requiring under two hours	50	63
Average crystalloids given in operating room	900 c.c.	400 c.c.
Average amount of blood given in operating room	300 c.c.	300 c.c.

In Table I it may be noted that the average age of the patients in each group is approximately the same. The percentage of the patients suffering from cancer is given, as this is an extremely important factor in the preoperative condition. Of the patients in the group having radical intestinal resections or other extensive major procedures the number of patients receiving each anesthetic is approximately the same. The "exploratory" cases include those patients in whom an exploratory abdominal operation revealed an inoperable condition, and cecostomy, gastrostomy, or only biopsy was done. Although these latter are not extensive procedures, they carry the gravest immediate prognosis because of the uniformly poor condition of such patients. The slightly greater length of time required for operations done under continuous spinal anesthesia is probably due to the fact that the surgeon felt less hurried by the condition of the patient. It is noted that more fluid was given intravenously in the operating room to the patients receiving continuous spinal anesthesia than to those receiving ether anesthesia. The explanation of this is that the administration is begun at the start of the operation in continuous spinal anesthesia and the blood given in these patients was preserved with an equal amount of dextrose-buffer-citrate solution. Previously, it had been given as citrated whole blood.

TABLE II

COMPARISON OF OPERATIVE AND POSTOPERATIVE COURSE (200 CASES)

	CONTINUOUS SPINAL ANESTHESIA	GENERAL ANESTHESIA
Satisfactory anesthetic and postanesthetic course	77	44
Satisfactory anesthesia with unrelated deaths (late)	2	3
Satisfactory anesthesia with postanesthetic disorientation	2	1
Satisfactory anesthesia with hypotension in operating room or postoperatively	10	34
Operative shock	2	10
Fatal shock	2	2
Postoperative atelectasis	1	1
Fatal bronchopneumonia (within three days postoperatively)	2	2
Fatal emboli	0	3
Severe postoperative headache	1	0

In Table II, evaluating the anesthetic and the postanesthetic course, a patient's condition was considered satisfactory if the vital signs remained unchanged throughout the time on the operating table and for twelve hours postoperatively and if no technical or anesthetic complications occurred.

Two patients receiving continuous spinal anesthesia and three patients receiving ether died after a gradual downhill course. All these deaths were in patients suffering from abdominal carcinomatosis demonstrated at operation, and their deaths are in no way referable to the anesthetic as such. Three patients became disoriented postoperatively, but all three were in subclinical uremia. This was felt to be the cause of their disorientation rather than the anesthetic. All three recovered.

Hypotension was defined for our purposes as a blood pressure fall in the operating room or within the first twelve hours postoperatively to a systolic level below 90 mm. mercury pressure, or a fall of more than one-third the systolic pressure in patients whose preoperative reading was over 150 systolic. This hypotension was not accompanied by pulse variation of great degree, nor in any instance did it last over ten minutes. It responded promptly to the administration of intravenous ephedrine or saline solution in the patients given continuous spinal anesthesia and to the administration of appropriate stimulants in those given general anesthetics. Patients who did not respond to these therapeutic measures but required transfusions were not considered to be suffering from hypotension but from shock and the results are listed separately.

In comparing the first 50 and the second 50 cases in which the patients were given continuous spinal anesthesia, it is found that eight of the ten episodes of hypotension occurred in the first 50 patients, and we feel that the case records in the latter group show a smoother and more nearly perfect anesthetic course and postoperative recovery.

In those previously considered groups we have the totals of 92 satisfactory continuous spinal and 81 satisfactory general anesthetics, which leads to the remainder of the patients in the series in whom complications were encountered.

Shock occurred in twelve patients. In those receiving continuous spinal anesthesia there were only two instances. Both occurred during bowel resection. In those given ether five occurred in bowel resection and five in massive major cases. The difference in favor of the continuous spinal anesthesia is probably due, in considerable part, to the security felt with this anesthetic in suspending all manipulation as soon as any blood pressure drop was reported until the vital signs had returned to normal. Review of the case records also gives the impression that in the patients given ether there was occasional hesitancy or

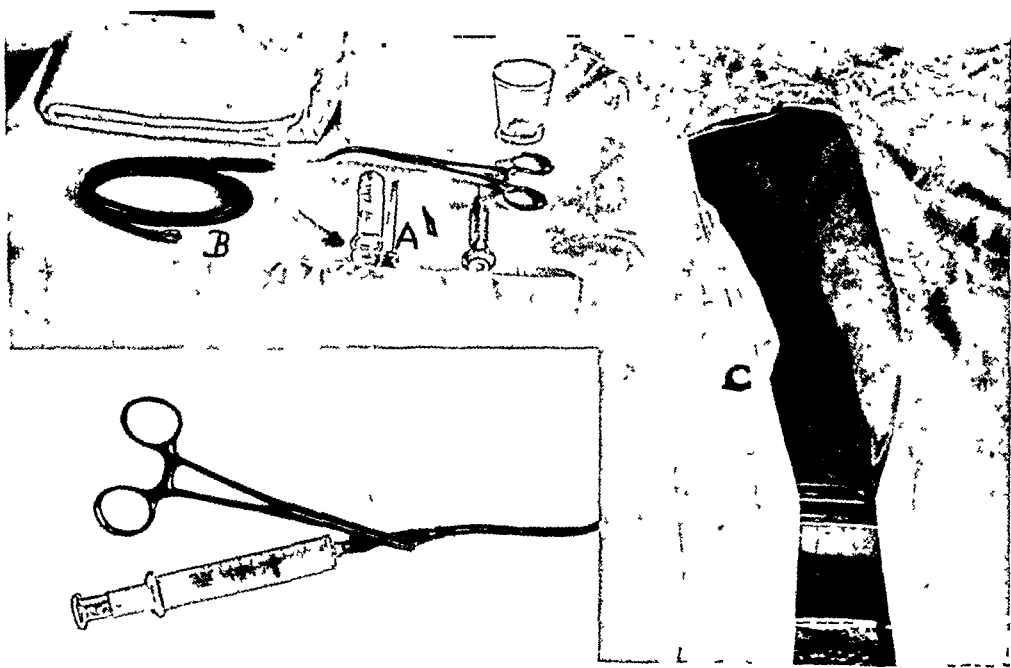


Fig 1—Continuous spinal anesthesia setup. Only special features are malleable spinal needle (A), fine bore rubber tubing (B), and thick mattress with space cut out to accommodate needle (C). Insert shows simple means of eliminating annoying stopcock by replacing with short length (1 1/4 inch) of gum tubing and clamp.

delay in giving blood, although the total amount given was usually the same. The patients were not given transfusions at the first suspicion of shock, some time occasionally elapsing before blood was started. A readily available source of this fluid, such as is provided by a blood bank, now obviates this difficulty. The routine preoperative cross-grouping of the patients with blood available in a bank and the placing of a cannula in a vein at the beginning of every operation allows greater ease and speed in the giving of a transfusion. In all fairness we feel that this prophylactic administration of blood is a

factor also partly responsible for the decreased number of cases of shock in the patients given continuous spinal anesthesia.

Four patients died in circulatory collapse, either during or shortly after the operative procedure. Two were in each group. Three of these patients had large bowel resections and one had a hemipelvectomy. In all instances the operative trauma and the poor preoperative

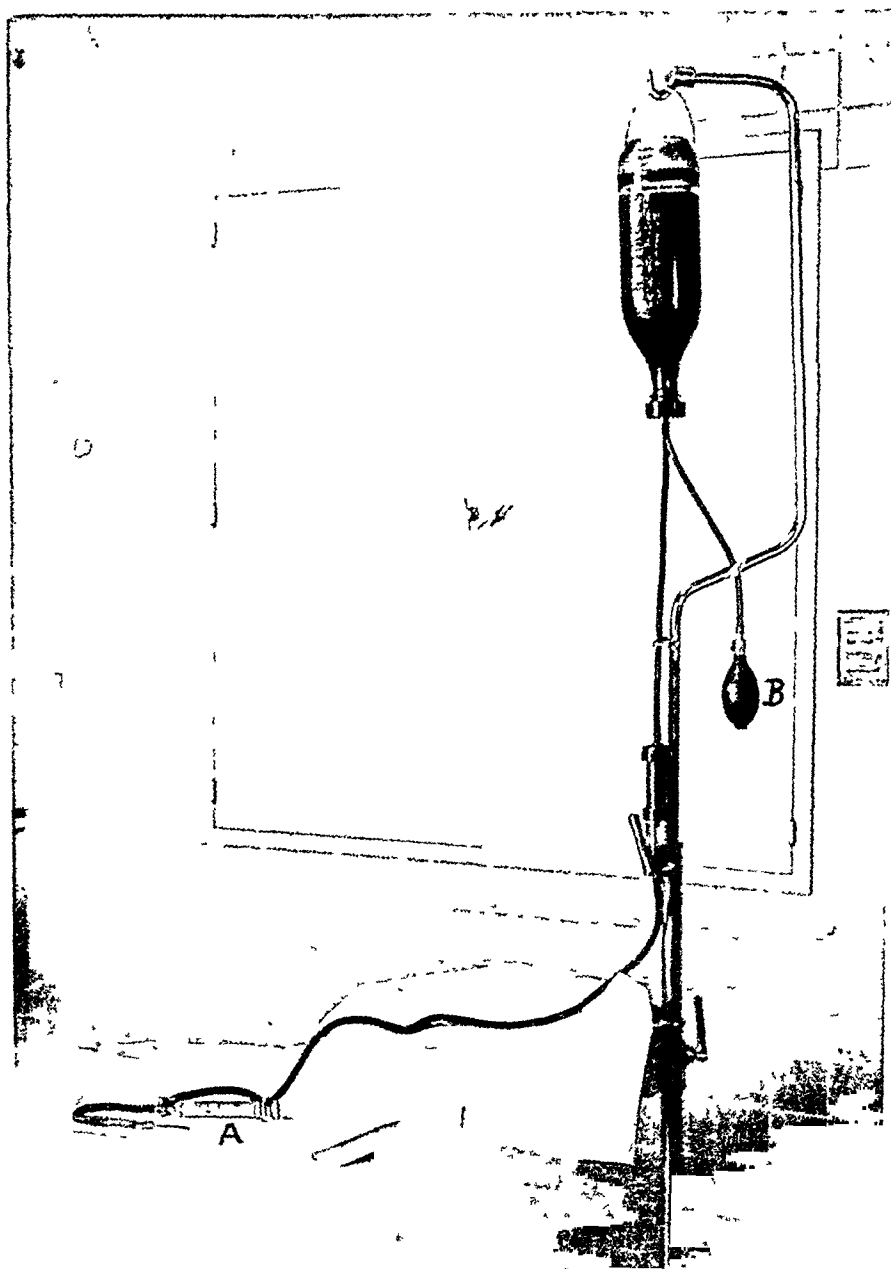


Fig 2—Intravenous apparatus which is always set up before continuous spinal anesthesia is begun in any major operation (A) Syringe in circuit for administration of ephedrine and pentothal (B) rubber bulb to provide for more rapid administration of blood or plasma as an occasion may demand

condition of the patient was sufficient to explain the fatality without implication of the anesthetic used.

The pulmonary complications were equal in each group and the incidence is not unduly high in either. The two patients developing clinical atelectasis had uneventful recoveries. The patients dying early of bronchopneumonia were all in the exploratory laparotomy group and were extremely poor operative risks. It is interesting that fatal emboli (proved at post-mortem examination) occurred in three patients given ether, whereas, none have so far been encountered in any of the patients given continuous spinal anesthetics (300) to date.

As to the complications peculiar to those given continuous spinal anesthesia, the patient who developed headache suffered severely from it for two weeks postoperatively with complete recovery. He also had headaches from a single dose of spinal anesthesia and would now be considered an unsuitable candidate for this method. In another patient (case not tabulated) the anesthetic solution leaked around the needle but good relaxation and loss of sensation was obtained. No difficulty followed except that an excessive amount of procaine had to be used.

The method by which continuous spinal anesthesia has been administered in these 100 patients and in the other 200 patients to whom we have given it is as follows:

In the operating room the apparatus and technique suggested by Lemmon,<sup>1</sup> with certain modifications to be discussed later, was used. Five per cent procaine was the anesthetic solution which we employed. Three and five-tenths per cent solution was tried previously and found inadequate as it did not produce a dependable level of anesthesia. Adjunctive sedation (not anesthesia) was secured with the intravenous administration of a 2.5 per cent solution of pentothal sodium. The anoxia present in old patients in poor condition under spinal anesthesia was combated by the administration of supplementary oxygen, 5 liters per minute. Intravenous administration of saline solution, blood transfusion, or plasma was used routinely to replace lost fluid.

The apparatus for continuous spinal anesthesia consists of a malleable No. 19 needle with a stylet. To this, a length of firm narrow lumen tubing is connected by an adaptor. The other end of the tubing is attached to a 10 c.c. syringe. A short (approximately 2 cm) piece of ordinary rubber tubing interposed between the syringe and the narrow tubing is used instead of a stopcock. A hemostat clamped across this controls flow of the anesthetic solution. When this large-gauge rubber tubing is worn out, it can be easily and cheaply replaced, and it never sticks or gets out of order as is often the case with the smaller metal valves. The introducer for the malleable needle is seldom used because leakage of spinal fluid seemed to occur around the needle tract when it had been used for skin puncture on thin or small patients; and if the director is incorrectly placed at the first attempt, readjust-



ment is traumatic and occasionally difficult. An ordinary stab blade to puncture the skin usually suffices and the malleable needle is then inserted without further aid.

The patient is placed in a lateral recumbent position on a mattress,\* which has a space under the lumbar region where the needle may late fit. The malleable needle is placed in the spinal canal in the third lumbar space for low abdominal procedures and in the second lumbar space for higher ones. The unsparing use of local 1 per cent procaine almost completely removes the discomforts of the puncture. Ten cubic centimeters of spinal fluid are removed and mixed with 500 mg. procaine. If more anesthetic solution is needed for longer procedures normal saline solution is used as a diluent. Either solution works well. The syringe is connected to the tubing and then to the spinal needle which has previously been placed in the spinal canal, after the air has been evacuated from the system. When, by testing, absolute free flow is assured, the patient is returned to the supine position with the neck acutely flexed. No anesthetic solution is given.

Under local anesthesia, a cannula is placed in a vein, preferably one in the ankle, and administration of intravenous saline solution begun. A catheter placed in the urinary bladder (this may be best done after anesthesia has been produced) and attached to a drainage bottle is used in all low abdominal procedures and in those upper abdominal procedures which may be long. The stomach tube, which is routinely inserted on the ward in patients in whom gastrointestinal surgery is planned, is opened and its free end allowed to drain into an emesis basin. A small intranasal catheter or mask is prepared for oxygen administration. The intranasal catheter is used when suction on the stomach tube may be necessary; otherwise, the mask is preferred. The vital signs are checked and the presence of free flow in the anesthetic solution system is confirmed. This is important because moving the patient may have affected the position of the needle, and adequate anesthesia is occasionally not obtained in the absence of absolute free flow. Ephedrine, 0.024 Gm., is injected into the intravenous tubing just before the procaine is to be administered. This routine and time of administration have, in our hands, proved to be the most satisfactory.

Now, 3 c.c. of the 5 per cent solution of procaine (150 mg.) are injected into the spinal canal. The patient is placed in 10-degree Trendelenburg position with the neck still acutely flexed and the desired level of anesthesia secured. At least 3 c.c. of procaine should be given if anesthesia to the nipple line is desired. The level of anesthesia rises slowly after the injection. Its progress is tested by following the gradual loss of response to pinpricks. When the desired extent of anesthesia is secured, usually within five minutes, the patient is returned to the level position. It is our clinical impression that this rise

---

\*Such as that manufactured by George P. Pilling & Son Co., Philadelphia, Pa.

of anesthesia may be slower in patients with abdominal distention. Once the zone has been established, it will remain stationary, even if the patient is put in extreme Trendelenberg position and more procaine injected. Lesser amounts of anesthetic solution than 3 c.c. for the initial dose do not seem to secure adequate anesthesia to the nipple line, and supplementary doses merely maintain, but do not raise, the level. This height of anesthesia is adequate for all abdominal procedures. Operations on the lower abdomen and the extremities do not, of course, require it. Even with anesthesia as high as the nipple line, the patients will become apprehensive or complain of discomfort when a hand is placed between the liver and the diaphragm. This discomfort is transitory and largely eliminated by the use of pentothal sodium intravenously. The pentothal sodium is introduced in a 2.5 per cent solution in normal saline into the intravenous tubing as needed for hypnosis during long operation. Judiciously used it relieves completely the discomfort attendant upon upper abdominal exploration and the ennui of a long interval of time which the patient must spend restrained and in one position. Yet reliance is not placed on the pentothal for anesthesia; its only use is as a control of sedation. Intermittent injection of 1 c.c. of procaine every twenty or thirty minutes (with some variations, dependent upon the procedure, age, size, and condition of the patient) will maintain the anesthesia. Five liters of oxygen per minute are administered through a mask or intranasal tube, because these patients have a diminished capacity for oxygen utilization due to emphysematous changes of age and the paralysis of the abdominal muscles of respiration. As soon as the anesthetic has reached the desired level, appropriate skin preparation and drape is performed and the operation may proceed.

The availability of pentothal sodium for intravenous administration relieves any concomitant discomfort which may go with the length of the procedure. The administration of oxygen intranasally prevents anoxia which might otherwise occur. In long operative procedures the patients have secreted from 300 to 700 c.c. of urine, which is carried off by the urinary catheter. The stomach tube is helpful in decompressing the stomach when air swallowing has occurred. As part of the routine preoperative preparation, each patient is cross-grouped and blood is available in the hospital bank. With an intravenous cannula in place in an ankle vein and saline solution slowly running, a transfusion may be started if desired within two or three minutes of the time such a decision is made. All these details are extremely important, and each is necessary in contributing to the sum total of operating room control which can be available.

Ephedrine, 0.024 Gm., is given intravenously as needed to combat the fall in blood pressure due to the procaine, but only that due to the procaine. After the initial dose additional doses of like amount will probably be needed with each subsequent administration of 50 mg. of

novocain. Should either the anesthetist or the surgeon suspect that the present or next contemplated surgical maneuver will initiate shock, a blood transfusion must be started at once. Giving blood in anticipation of shock saves more lives than all therapeutic measures possible after collapse has become manifest. The differentiation of hypotension due to surgical shock and that due to procaine may be difficult at times but is usually evident from the facts at hand. If the blood pressure does not respond at once to 0.024 Gm. of ephedrine intravenously, the fall must be attributed to surgical shock and be so treated.

Postoperatively the employment of carbon dioxide inhalation, routine transfusions, low Fowler's position as indicated, and watchful care must be assured the patient as in general anesthesia. The details of this need not be elaborated here.

#### DISCUSSION

The introduction of the continuous principle into spinal anesthesia has made it possible to continue operations under spinal block for previously unheard of lengths of time. In a sense this has meant redevelopment of much of the technique of spinal anesthesia. Some of the factors requiring more attention as the result of the increased length of anesthesia were adequate oxygenation and aeration of the patient, control of blood pressure drops, and elimination of discomfort for these long periods. All of the cases presented here in which the patients received continuous spinal anesthesia were observed during this period of development which, to a more limited degree, is still continuing.

Resultant improvement in the management of the patients given spinal anesthesia is reflected in a limited comparison between the first and last 50 cases presented. All of the general anesthetics given were based on long experience with this method, so that it seems likely that the superiority of continuous spinal anesthesia is apt to become still more apparent than is indicated by this presentation as our acquaintance with it grows. We believe that the excellence of continuous spinal anesthesia is due primarily to three factors:

First, relaxation is sustained and complete, necessitating considerably less operative trauma. This is attested to by the fact that no fatal emboli occurred in the patients given spinal anesthesia as compared to three in those given ether anesthesia. Moreover, during unforeseen accidents, such as hemorrhage or gross spillage, maintenance of exposure and protective packs can be depended on.

Second, the surgeon is never hurried. Extensive and lengthy procedures are, unfortunately, most often necessary in patients whose general condition is least able to withstand them. On such occasions it is extremely gratifying to the surgeon to be able to take time for careful thought and meticulous work without regard to the duration of anesthesia. If surgical trauma becomes excessive and the blood

pressure drops, it has become our custom to suspend work immediately while blood or plasma is administered more rapidly and the patient is given ample opportunity to recover.

Finally, continuous spinal anesthesia is particularly advantageous in patients with cancer because it inherently provides for the element of uncertainty in all exploratory procedures where the operability must remain in question until the peritoneum has been opened. In the inoperable patient the small initial dose shortly wears off, returning the patient, with the exception of the incision, to his original preoperative state. In the operable case, provision is made for continuing unhurriedly as long as is necessary regardless of unforeseen difficulties.

#### SUMMARY

1. The results in 100 consecutive patients receiving general ether anesthesia and in 100 consecutive patients receiving continuous spinal anesthesia have been comparatively presented. It is felt that the relative constancy of all factors, with the exception of the type of anesthetic used, makes these unusually good groups for comparison.

2. On critical analysis, 44 per cent of the patients given general anesthesia and 77 per cent of those given continuous spinal anesthesia were considered to have had satisfactory operative and postoperative courses. The incidence of blood pressure falls was very appreciably less in those who received spinal anesthesia, with definite improvement in technique reflected in the course of the first and last fifty patients so treated. The occurrence of three fatal pulmonary emboli following the use of general ether anesthesia and none following the use of continuous spinal anesthesia, in our opinion, reflects the less complete relaxation produced by the former, necessitating greater operative trauma.

3. Our method of administration of continuous spinal anesthesia is similar to that described by Lemmon, with certain simplifying modifications. The management of these patients, involving considerably more than the periodic administration of a spinal anesthetic agent, is discussed from several of its important aspects.

## CYSTOMETRY AFTER SPINAL ANESTHESIA

MAJOR CARROLL J. BELLIS, MEDICAL CORPS RES., U. S. ARMY

### INTRODUCTION

CREEVY'S classical studies of the effects of prolonged vesical distention demonstrated that profound irreversible urinary tract damage may follow the neglect of the overdistended bladder. In the presence of urinary retention, there is an increased susceptibility of the urinary tract to infection; in fact, patients who were thought to have succumbed to obscure vasomotor effects following rapid decompression of the chronically distended bladder or to the infection attending catheterization really have died as a result of latent upper urinary tract infection harbored prior to the emptying procedure.<sup>20</sup>

Every cystoscopist is familiar with the mural hemorrhages in the acutely or chronically distended bladder (Mercier,<sup>50</sup> Grellety,<sup>34</sup> Picard,<sup>56</sup> Tuffier,<sup>54</sup> Genouville and Boeckel,<sup>29</sup> Delbet,<sup>27</sup> Chute,<sup>18</sup> and Vintici and Laroche<sup>76</sup>). Creevy<sup>21</sup> and others (Shigematsu,<sup>70</sup> and Guyon and Albaran<sup>36</sup>) have demonstrated these hemorrhages within forty-eight hours, by which time the postural tone (a protective mechanism) has failed, gangrene and perforation intervening in sixty to seventy-two hours. The hemorrhages occur first in the submucosa of the bladder, then occupy the entire wall and proceed up to the kidney. Thus, urinary retention produces increased susceptibility of the urinary tract to infection. Creevy says, "The necrotic tissue furnishes a culture medium the surface of which is isolated from the usual defenses against bacterial invasion; the loss of contractility causes incomplete emptying of the bladder. The resultant stasis favors bacterial growth."

Indeed, this sequence of events was described as early as 1873 by Goodheart.<sup>32</sup> Others (Achard and Regnault,<sup>1</sup> Albarran and Halle,<sup>3</sup> Bazy,<sup>4</sup> Melchior,<sup>48</sup> Rovsing,<sup>64</sup> and Schmidt and Aschoff<sup>65</sup>) have shown that virulent bacteria injected into the intact bladder are harmless until the bladder is traumatized or obstructed, whereupon severe infection of the bladder and upper urinary tract often develops.

When a measurable quantity of urine is present in the bladder, the intravesical tension is 6 to 10 cm. water (Boeminghaus,<sup>7, 8</sup> Mosso and Pellacani,<sup>51</sup> and Rose<sup>61</sup>). When the volume reaches 200 to 400 c.c., the pressure quite abruptly rises to 18 to 30 cm. water, the exact figure being different for different authors (Hirsch,<sup>48</sup> Kreutzmann,<sup>40</sup> Pilcher,<sup>57</sup> Schwarz and Brenner<sup>66</sup>), and a desire to urinate, coinciding with mild rhythmic contractions of the detrusor and relaxation of the internal sphincter, is established.

The human detrusor urinae is probably incapable of exerting a pressure much more than 40 cm. water, the intravesical tension maintaining a fairly constant degree of pressure within wide limits of filling. This ability of the bladder to relax as it fills, maintaining a constant pressure, was designated by Sherrington<sup>65, 66</sup> as "postural tone." However, this pressure is raised remarkably in acute urinary retention, with resulting damage due to the intermittent attempts to void, which may produce considerable rises in intravesical tension (Creedy<sup>22</sup>).

Creedy<sup>24</sup> has pointed out that the inability to void after surgical operations is due to the horizontal position of the patient, the pain of the injured tissues, and drugs, such as the anesthetic or opiate. He has emphasized the importance of early catheterization, if spontaneous voiding six to eight hours after the previous voiding is impossible. He correctly has pointed out the fallacy of relying on cholinergic, vagotropic, or parasympathomimetic drugs or such artifices as audible running water to produce voiding. More often than not, urine so obtained is merely an overflow. A more physiologic emptying may be permitted through a small sterile, well-lubricated catheter, passed gently and frequently enough, or simply left in place for a day.

#### PURPOSE OF THE STUDY

Although the acute urinary retention secondary to many operations, such as the post-partum state (Bennetts and Judd<sup>6</sup>), and to laparotomies is a familiar picture, no studies have been recorded of the effects of such procedures or the anesthetics per se on the cystometrogram. The measurements to be described were undertaken with the view of determining the relationship between desire to void, intravesical tension at that point, and the bladder volume required in the immediate postanesthetic period.

Varying figures have been published purporting to represent the pressure in the distended bladder. Dubois<sup>28</sup> stated that the pressure was 9 to 10 cm. water; Pilcher<sup>57</sup> gives it as 26 to 30 cm. water; Campbell<sup>15</sup> found the average of eleven cases to be 28 cm. water; Bumpus and Foulds<sup>14</sup> found it to be 50 cm. water. Watkins,<sup>78</sup> using large quantities of filling fluid, found that a progressive rise in bladder pressure took place with filling. From the work of Mellanby and Pratt,<sup>49</sup> and Boyd and Smith,<sup>9</sup> it appears that a progressive rise does not take place under physiologic conditions.

It becomes apparent, then, that one must employ a method of cystometry which would approximate normal conditions. For this purpose ninety-four young men, none of whom had any apparent urologic disease, with ages ranging from 18 to 35 years, were selected. These soldiers were operated on under spinal anesthesia for the conditions listed in Table I, cystometrograms being made as soon as sensation below the level of anesthetic injection returned. Consequently, in

TABLE 1

DISTRIBUTION OF OPERATIONS AMONG CASES USED FOR CYSTOMETRIC STUDY

SURGICAL PROCEDURE	NUMBER OF CASES
<i>Spinal Anesthesia</i>	
Hemorrhoidectomy	18
Pilonidal cystectomy	42
Appendectomy	8
Rectopexy	2
Inguinal herniorrhaphy	8
Débridement of foot	2
Hydrocelectomy	2
Anal fistulotomy	4
Curettement, actinomycosis of inguinal region	1
Meniscectomy (knee)	2
Colectomy	1
Preparation of abdominal tubed pedicle graft	1
Pinch grafts from abdomen	3
Total	94
<i>Intravenous Pentothal Sodium Anesthesia</i>	
Incision and drainage of abdominal wall abscess	1
Curettement, actinomycosis of neck	1
Divulsion of anorectum for stricture	1
Manipulation of knee	1
Reduction of dislocated ankle	1
Total	5

nearly every case, the determination was made within two hours after the patient's return from the operating room.

The principles of cystometry and the interpretation of cystometrograms have been adequately discussed elsewhere. (McCrea,<sup>47</sup> Lewis and Langworthy,<sup>43</sup> O'Heeron,<sup>55</sup> Simons,<sup>72</sup> Cheetham,<sup>17</sup> Boyd and Smith,<sup>10</sup> Weyrauch and Peterfy,<sup>79</sup> and Wood.<sup>60</sup>) In addition many types of cystometers have been described (Cone and Bridgers,<sup>19</sup> Valk,<sup>75</sup> Davidson,<sup>26</sup> Simons,<sup>71</sup> Lewis,<sup>42</sup> Povlsen,<sup>58</sup> Brodie, Helfert, and Phifer,<sup>11</sup> Carleton and Nagamatsu,<sup>16</sup> Lich and Ortner,<sup>41</sup> Greenberger and Helfert,<sup>33</sup> Muschat,<sup>53</sup> and Landes and Voris.<sup>41</sup>)

The procedure followed in this investigation was similar to that suggested by Rose.<sup>60, 62, 63</sup> A small whistle-tip catheter, No. 12 or 14F, was passed into the bladder and anchored to the penis with a single strip of adhesive tape, the bladder being allowed to empty. The catheter was then attached to the inlet tube (C) of the cystometer (Fig. 1) which is a three-outlet Carrel-Dakin tube of the tidal irrigator described previously (Bellis<sup>6</sup>). The Murphy drip (D) permits a continuous flow of measurable quantities of saturated boric acid solution from the reservoir (R) at the rate of about four drops per second, which is roughly equivalent to 15 c.c. per minute. Fluctuations of intravesical pressure, indicative of bladder contractions, are clearly visible in the upright glass manometer tube (M). In each case the pressure developed with each 20 c.c. of added fluid was recorded. The intravesical pressure and bladder volume were noted when the patient

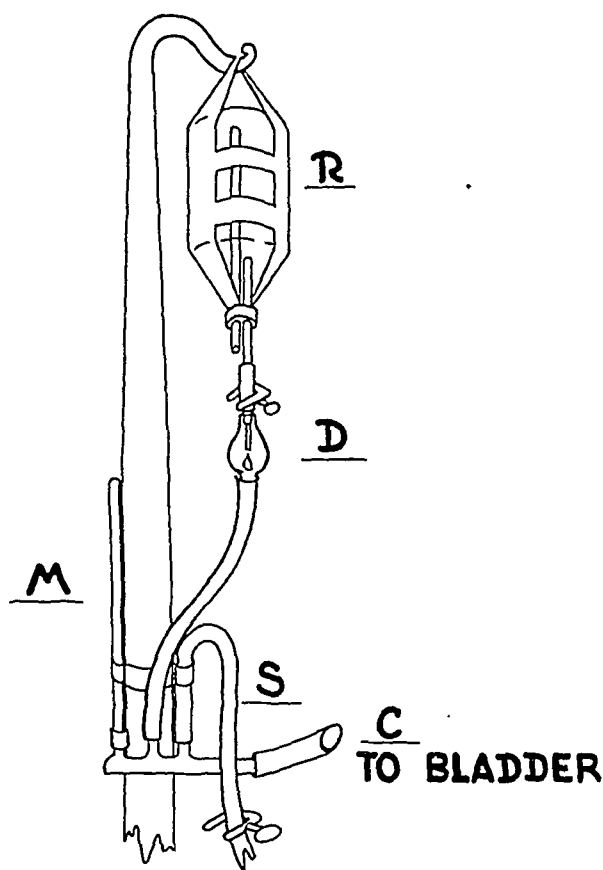


Fig. 1.—Tidal irrigator converted to cystometer. *R*, reservoir; *D*, Murphy drip; *M*, manometer; *S*, siphon; and *C*, catheter tubing.

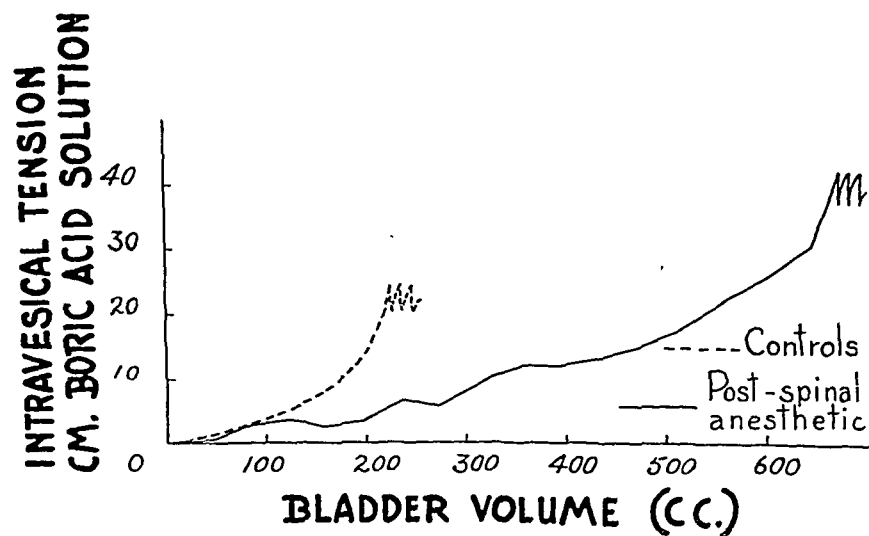


Fig. 2.—Effect of spinal anesthesia on mean intravesical tension developed with increasing bladder volume.



indicated a desire to void, attended by the development of pain and such marked bladder contractions that fluid was expelled around the catheter. The cystometry was then discontinued, the bladder fluid siphoned off (S), and the catheter removed. Many of the patients were given injections of morphine during the cystometry because of postoperative pain. Although the cystometrograms in such cases may have been slightly altered by the narcotic, the modification of the readings obtained are probably not important.

Control determinations were made on five patients who had been given intravenous pentothal sodium as anesthesia for very short operations. In these cases, it was necessary that the cystometry be performed in two to three hours postoperatively in order to allow for recovery from the anesthetic.

### RESULTS

The study showed a surprising uniformity of measurements. Generally, in the spinal anesthetic group, the intravesical tension increased slowly as the bladder was distended with fluid, the strong rhythmic contractions, indicated by fluctuations in the manometer column, coincident with desire to void, occurring at greater volumes and at higher pressures than in the controls. The mean volume of solution required to produce a desire to void in the spinal series was 671 c.c. the mean intravesical tension at that point being 42 cm. water (Fig. 2). The small rhythmic vesical contractions during filling described by Goltz<sup>31</sup>

TABLE II  
MEAN INTRAVESICAL TENSIONS CORRESPONDING TO BLADDER VOLUMES

BLADDER VOLUME (C.C.)	INTRAVESICAL TENSION (CM. BORIC ACID SOLUTION)
<i>Spinal Anesthetic Group</i>	
40	1
80	3
120	4
160	3
200	4
240	7
280	6
320	10
360	12
400	12
440	13
480	14
520	16
560	22
600	25
640	31
671	42
<i>Control Group</i>	
40	2
80	3
120	6
160	9
200	12
224	24

in the dog were also observed in these patients. The greatest volume of solution required to produce strong bladder contractions and a desire to void was 1,340 c.c., the pressure developed being 41 cm. water. The least volume of solution required was 480 c.c., the intravesical tension at that distention being 21 cm. water.

In the control group, the mean bladder volume at which desire to void was experienced was 224 c.c., the mean intravesical tension at that volume being 24 cm. water (Fig. 2). The greatest bladder volume necessary to produce a desire to void was 260 c.c., the tension at that volume being 28 c.c.

In both groups the intravesical tension rose slowly as fluid was added to the bladder. However, as the point where desire to void was approached, the intravesical tension rose rapidly, giving a parabolic, rather than a logarithmic type of curve (Table II).

#### DISCUSSION

It is well known that lesions of the central nervous system which disturb sensation of the bladder disturb its voluntary control (Curling<sup>25</sup>). Consequently, the use of the cystometrogram in the study of neurogenic vesical dysfunction has received wide recognition (Smith and Engel,<sup>73</sup> Magid,<sup>45</sup> Adams,<sup>2</sup> Voris and Landes,<sup>77</sup> Muschat,<sup>54</sup> and Munro and Hahn<sup>52</sup>). Not one investigator in this field has failed to emphasize that when sensation from the bladder is lost, its postural tonus arcs are interrupted, leading to overdistention with absence of desire to urinate, even at abnormally high intravesical tensions. If this state is allowed to persist even for a few hours, bladder sensation is further obtunded, aggravating the cycle. Shatlock<sup>67</sup> demonstrated a temporary retention and overflow incontinence in the cat after cocaineization of the bladder mucosa. More recently, Kirwin and Hawes<sup>39</sup> showed that in six young men who had voided after retaining their urine as long as possible and who were catheterized after finally urinating, residuals of 70 to 365 c.c. were present. Thus, even the vesical distention produced by voluntary retention may produce pressure anesthesia of the bladder wall.

Since the stretch reflex for the bladder is in the sacral cord (Budge,<sup>12, 13</sup> Giannuzzi,<sup>30</sup> and McClintic<sup>46</sup>), it is not surprising that residual vesical effects are found after the use of spinal anesthesia. Rehfishch<sup>59</sup> showed that urinary continence is a matter of mural tonus rather than sphincter action, and although this concept is somewhat modified today from our knowledge of the anatomic disposition of the internal sphincter, it still remains that sphincter action is not the most important mechanism in continence.

Creevy,<sup>23</sup> Gruber,<sup>35</sup> and Hibbs<sup>37</sup> have fully described the innervation of the bladder in relation to micturition. The internal sphincter itself is probably a specialization of the detrusor urinae, while the external

sphincter, lying between the layers of the urogenital diaphragm, consists of the sphincter urogenitalis urethrae and the transversus perinei profundus, contracting as a unit.

The pudic (pudendal) nerves arising from the first three or four sacral segments are sensory for the urethra and motor to the external sphincter. The pelvic nerves (*nervus erigens*), also arising from the first three or four sacral segments, are parasympathetic and sensory, carrying sensory impulses from the bladder wall and motor impulses to it through the terminal ganglia of the vesical plexus. Being motor to the detrusor, they also cause the internal sphincter to open.

The hypogastric nerves (presacral) are physiologically sympathetic, arising from the second to fifth lumbar segments, proceeding by way of synapses in the inferior mesenteric ganglia and the postganglionic fibers to form the lower ganglia of the abdominal sympathetic trunk. According to Creevy, a few preganglionic fibers from the aortic plexus have synapses in the ganglia of the vesical wall. Although about 25 per cent of the fibers of the hypogastric plexus are sensory, the primary function of the hypogastric nerves is to inhibit the detrusor, and, hence, they have been called the "nerves of bladder filling." Although there may be a myogenic contraction of the detrusor, as seen occasionally in neglected cases of neurogenic vesical dysfunction with overflow incontinence, there are two principal centers for micturition: (1) bilaterally symmetrical in the brain, and (2) in the spinal cord and vesical plexus.

Therefore, urinary retention may be caused by an irritative motor lesion producing sphincter spasm, or it may result from detrusor paralysis, usually from loss of sensation rather than from motor paralysis per se. The result of distention, as seen in overflow incontinence, is a rise of intravesical tension to a destructive level, with dilation of the ureters and kidney pelves, hydronephrotic atrophy, and uremia.

Spinal anesthesia temporarily establishes a type of neurogenic vesical dysfunction, probably due to the anesthetic agent. The bladder wall remains somewhat insensitive to its distending contents, and although the expulsive force of the detrusor may actually not be diminished, the normal strong reflex vesical contractions, which coincide with desire to void, do not appear until the volume of the bladder and the intravesical tension are so great as to invite further pressure anesthesia of the wall, and a continued sensory type of retention which initiates urinary infection.

To wait until the bladder is distended to these levels is to court infection. If malaise, chills, fever, and leucocytosis follow catheterization after the bladder has been so distended, the blame need not be placed on the catheter. The surgeon must call himself to task for allowing the seeds of infection to become implanted in the bladder wall by permitting distention, pressure necrosis, retention, and reduced sensitivity to pursue their vicious cycle. Early catheterization

of patients after administration of spinal anesthesia, and, perhaps, after inhalation anesthesia, is a necessary therapeutic adjunct.

The surgeon must be mindful of the hour at which the bladder was emptied preoperatively, the diuretic effect of the sympathetic-paralyzing anesthetics, and the fluids administered postoperatively. Often, a patient will require catheterization four or five hours after returning from the operating room, where operation, perhaps of one hour, has been performed, and following which intravenous solutions have been administered. Merely to direct a subordinate to "catheterize in twelve hours if patient has not voided," is a fateful and foreboding procrastination. Early catheterization, by preventing pressure anesthesia of the bladder wall, will facilitate early subsequent spontaneous voiding, while delayed or widely-spaced catheterizations serve to aggravate the neurogenic dysfunction and precipitate infection.

#### SUMMARY

Cystometrograms were made in ninety-four surgical patients immediately after cessation of spinal anesthesia. It was found that the mean volume of solution and the corresponding mean intravesical pressure required to produce desire to void were extremely high (671 c.c. at 42 cm. water) compared with controls having received intravenous anesthesia. In no case were the intravesical volume and tension within normal limits. This is interpreted to mean that following the use of spinal anesthesia there remains a residual mural insensitivity, coexistent with a decrease in vesical tone.

These observations are discussed in the light of the neurophysiology of micturition and the dangers attending delay in catheterization of the postspinal anesthetic patient.

#### REFERENCES

1. Achard, C., and Regnault, J.: Sur les rapports du *Bacterium coli commune* avec le *Bacterium pyogenes* des infections urinaires, *Compt. rend. Soc. de biol.*, Paris 43: 830, 1891.
2. Adams, P. S.: Use of Cystometer in Diagnosis of Neurogenic Bladders (With Comments on Treatment and Case Reports), *Nebraska M. J.* 23: 63, 1938.
3. Albarran, J., and Halle, N.: Note sur une bactérie pyogène et sur son rôle dans l'infection, *Bull. Acad. de méd.*, Paris 20: 310, 1888.
4. Bazy: Note sur le pathogénie, le diagnostic, et le traitement des pyélonéphrites suppurées., *Bull. et mém. Soc. nat. de chir.* 22: 263, 1896.
5. Bellis, C. J.: An Improved Apparatus for Tidal Drainage of the Urinary Bladder and Empyema Cavities, *SURGERY* 8: 791, 1940.
6. Bennetts, F. A., and Judd, G. E.: The Post-Partum Bladder, *Am. J. Obst. & Gynec.* 42: 419, 1941.
7. Boeminghaus, H.: Zur Feststellung des Einflusses der Blasenfüllung auf die Funktion der Nieren, *Deutsche. med. Wchnschr.* 51: 138, 1925.
8. Boeminghaus, H.: Ueber funktionelle Zusammenhänge zwischen Harnblase und Niere (vesico-renal Reflex), *Arch. f. klin. Chir.* 154: 114, 1929.
9. Boyd, M. L., and Smith, W. A.: Why Are Abnormal Cystometrograms Obtained in Normal Patients? *J. Urol.* 40: 513, 1938.
10. Boyd, M. L., and Smith, W. A.: Are Cystometrograms Indispensable for Explanation of Function Disturbances? *J. Urol.* 42: 410, 1939.
11. Brodie, E. L., Helfert, I., and Phifer, I. A.: Cystometric Observations in Neurosyphilis, *Urol. & Cutan. Rev.* 43: 51, 1939.

12. Budge, J.: Ueber das Centrum genitospinale des Nervus sympathicus, Virchows Arch. f. path. Anat. 15: 115, 1858.
13. Budge, J.: Zur Physiologie des Blasenschliessmuskels, Arch. f. d. ges. Physiol. 6: 306, 1872.
14. Bumpus, H. C., Jr., and Foulds, G. S.: Gradual Emptying of the Overdistended Bladder, J. A. M. A. 81: 821, 1923.
15. Campbell, M. F.: Studies in Bladder Decompression, J. Urol. 17: 371, 1927.
16. Carleton, S., and Nagamatsu, G. R.: A New Cystometer, J. Urol. 41: 941, 1939.
17. Cheetham, J. G.: Clinical Evaluation of Cystometer, J. Urol. 39: 569, 1938.
18. Chute, A. L.: Observations on Cases of Prostatic Obstruction Presenting Overdistended Bladders, Boston M. & S. J. 167: 607, 1912.
19. Cone, W. V., and Bridgers, W. H.: Combined Tidal Irrigator and Cystometer for Management of the Paralyzed Bladder, Surg., Gynec. & Obst. 75: 61, 1942.
20. Creevy, C. D.: Sudden Decompression of the Chronically Distended Urinary Bladder, Arch. Surg. 25: 356, 1932.
21. Creevy, C. D.: Distention of the Urinary Bladder. I. Hematuria and Sudden Emptying; an Experimental and Clinical Study, Arch. Surg. 28: 948, 1934.
22. Creevy, C. D.: Vesical Distention. Effects on the Motor Mechanism of the Upper Urinary Tract; An Experimental Study, Arch. Surg. 29: 723, 1934.
23. Creevy, C. D.: Neurogenic Vesical Dysfunction. Alterations in the Physiology of Micturition Due to Lesions of the Nervous System, Arch. Neurol. & Psychiat. 34: 777, 1935.
24. Creevy, C. D.: The Care of the Urinary Bladder After Operation, SURGERY 7: 423, 1940.
25. Curling, H. B.: Affections of the Urinary Bladder in Paraplegia, London Med. Gaz. 13: 353, 1833.
26. Davidson, O. W.: A Practical Cystometer, J. Urol. 40: 452, 1938.
27. Delbet, P.: Rétention et incontinence d'urine; in Pousson, A., and Desnos, E.: Encyclopédie française d'urologie, vol. 6, Paris, 1914, Gaston Doin & Cie, p. 492.
28. Dubois, P.: Ueber den Druck in der Harnblase, Dent. Arch. f. klin. Med. 17: 148, 1876.
29. Genouville, M., and Boeckel, A.: Physiologie pathologique du cathétérisme; in Pousson, A., and Desnos, E.: Encyclopédie française d'urologie, vol. 4, Paris, 1914, Gaston Doin & Cie, p. 944.
30. Giannuzzi: Recherches physiologiques sur les nerfs moteurs de la vessie, J. physiol. de l'homme. 6: 22, 1863.
31. Goltz, F.: Ueber die Funktionen des Lendenmarks des Hundes, Arch. f. d. ges. Physiol. 8: 460, 1874.
32. Goodheart, J. F.: On Erysipelas of the Kidney and Urinary Tract, Guy's Hosp. Rep. 19: 357, 1873.
33. Greenberger, M. E., and Helfert, I.: Cystometric Observations in Tuberculous Bladders, Quart. Bull., Sea View Hosp. 5: 415, 1940.
34. Grellety, M.: Mécanisme des accidents mortels qui dans certains cas accompagnent l'évacuation trop prompte de la vessie, France méd. 25: 146, 1879.
35. Gruber, C. M.: The Autonomic Innervation of the Genito-Urinary System, Physiol. Rev. 13: 497, 1933.
36. Guyon, J. F., and Albarran, J.: Anatomie et physiologie de la rétention d'urine, Arch. de méd. expér. et d'anat. 2: 181, 1890.
37. Hibbs, D. K.: Physiology of Micturition, Urol. & Cutan. Rev. 43: 257, 1939.
38. Hirsch, E. W.: Relation of Bladder Pressure to Bladder Function, J. A. M. A. 91: 772, 1928.
39. Kirwin, T. J., and Hawes, G. A.: The Diagnostic Value of Residual Urine Examinations, J. Urol. 41: 413, 1939.
40. Krentzmann, H. A. R.: Studies in Normal Ureteral and Vesical Pressure, J. Urol. 19: 517, 1928.
41. Landes, H. E., and Voris, H. C.: A New Cystometer, Incorporating Advantage of Water Manometer and Continuous Tracing, J. Urol. 39: 813, 1938.
42. Lewis, L. G.: A New Clinical Recording Cystometer, J. Urol. 41: 638, 1939.
43. Lewis, L. G., and Langworthy, O. R.: Cystometry, J. Urol. 40: 677, 1938.
44. Lich, R., Jr., and Ortnier, A. B.: Economical Two-Way Catheter for Cystometry, Urol. & Cutan. Rev. 44: 616, 1940.
45. Magid, M. A.: Value of Cystometric Studies in Atonic Bladder, Rocky Mountain M. J. 35: 299, 1938.
46. McClintic, C. F.: The Clinical Neurophysiology of the Autonomic Urinary Bladder and Enureses, J. Urol. 20: 267, 1928.
47. McCrea, L. E.: Cystometry and Its Interpretation. Urol. & Cutan. Rev. 44: 362, 1940.

48. Melchior, M.: Berichte über 52 bakteriologische untersuchte Fälle von infectiöse Erkrankungen der Harntracte, Monatsb. d. Krankh. d. Harn. u. Sex.-Appar. 3: 584, 1898.
49. Mellanby, J., and Pratt, C. L. G.: Reactions of Bladder of Cat Under Conditions of Constant Pressure, Proc. Roy. Soc., London, s. B. 127: 307, 1939.
50. Mercier, A.: Note sur l'hématurie qui suit le cathétérisme dans quelques cas de rétention d'urine, Union. med. de Paris 9: 41, 1861.
51. Mosso, A., and Pellacani, P.: Sur les fonctions de la vessie, Arch. ital. de biol. 1: 97, 291, 1882.
52. Munro, D., and Hahn, J.: Tidal Drainage of the Urinary Bladder, New England J. Med. 212: 229, 1935.
53. Muschat, M.: Simplified Determination and Practical Interpretation in Cystometry; Critique of Attempts Made to Complicate This Procedure, J. Urol. 43: 582, 1940.
54. Muschat, M.: Cystometric Timing of Catheter Removal From a Neurogenic Bladder, SURGERY 7: 710, 1940.
55. O'Heeron, M. K.: Cystometry; Value and Limitations, J. Urol. 47: 824, 1942.
56. Picard, M.: Les dangers du cathétérisme chez les vieillards, France méd. 26: 106, 1879.
57. Pilcher, P. M.: Prostatectomy in Two Stages, Ann. Surg. 59: 500, 1914.
58. Povlsen, O.: Cystometric Technik, Ztschr. f. urol. Chir. u. Gynäk. 45: 72, 1939.
59. Rehfish, E.: Ueber den Mechanismus des Harnblasenverschlusses und der Harnentleerung, Virchows Arch. f. path. Anat. 150: 111, 1897.
60. Rose, D. K.: Cystometric Bladder Pressure Determinations, J. Urol. 17: 487, 1927.
61. Rose, D. K.: Clinical Application of Bladder Physiology, J. Urol. 26: 91, 1931.
62. Rose, D. K.: Various Cystometrograms and Their Interpretation, J. Urol. 27: 207, 1932.
63. Rose, D. K.: An Improved Continuous Flow Recording Cystometer, J. Urol. 43: 718, 1940.
64. Rovsing, T.: Aetiologie, Pathogenese, und Behandlung der septic Infektion der Harnwege, Monatsb. d. Krankh. d. Harn. u. Sex.-Appar. 3: 506, 1898.
65. Schmidt, M. B., and Aschoff, L.: Die Pyelonephritis in anatomischer und bakteriologischer Beziehung und die ursächliche Bedeutung der Bakterium coli commune für die Erkrankung der Harnwege, Jena, 1893, Gustav Fischer.
66. Schwarz, O., and Brenner, A.: Untersuchungen ueber die Physiologie und Pathologie der Blasenfunktion, Ztschr. f. urol. Chir. 8: 32, 1921.
67. Shatlock, S. G.: Is There an Idiopathic Dilatation of the Urinary Bladder? Proc. Roy. Soc. Med. (Sect. Path.) 2: 88, 1908.
68. Sherrington, C. S.: The Lumbo-Sacral Plexus, J. Physiol. 13: 678, 1892.
69. Sherrington, C. S.: Postural Activity of Muscle and Nerve: ii Visceral Muscle, Brain 38: 213, 1915.
70. Shigematsu, H.: Etude expérimentelle de la retention d'urine, J. d'urol. 25: 16, 1922.
71. Simons, J.: Neurologic Studies by Means of Microcystometer and Sphincterometer; Studies in Bladder Function (preliminary report), J. Urol. 39: 791, 1938.
72. Simons, J.: Cystometry; Status and Outlook, With Special Reference to Microcystometry and Sphincterometry, Urol. & Cutan. Rev. 42: 316, 1938.
73. Smith, C. K., and Engel, L. P.: Neurogenic Vesical Dysfunction in Children, J. Urol. 28: 675, 1932.
74. Tuffier, T.: Rôle de la congestion dans les maladies des voies urinaires, Thèse de Paris, 1885, p. 149.
75. Valk, W. L.: A Simple and Inexpensive Cystometer, J. Urol. 47: 838, 1942.
76. Vintici, V., and Laroche, A.: Hemorrhagies de la prostate, J. d'urol. 28: 140, 1929.
77. Voris, H. C., and Landes, H. E.: Cystometric Studies in Cases of Neurologic Disease, Arch. Neurol. & Psychiat. 44: 118, 1940.
78. Watkins, K. H.: The Clinical Value of Bladder Pressure Estimations, Brit. J. Urol. 6: 104, 1934.
79. Weyrauch, H. M., Jr., and Peterfy, R. A.: Tests for Leakage in Early Diagnosis of Ruptured Bladder; Use of Cystometrogram, J. Urol. 44: 264, 1940.
80. Wood, L. G.: Cystometry, Bull. Vancouver M. A. 17: 299, 1941.

# A DEMONSTRATION OF TWO TYPES OF BURN SHOCK

MYRON PRINZMETAL, M.D., H. C. BERGMAN, PH.D., AND  
OSCAR HECHTER, PH.D., LOS ANGELES, CALIF.

(From the Straus Research Laboratory, Cedars of Lebanon Hospital, and the  
University of Southern California Medical School)

IT HAS been recently shown that shock due to muscle injury can be produced through at least two different mechanisms: (1) local fluid loss, as demonstrated by Blalock,<sup>1</sup> and (2) a toxic factor, bacterial in origin.<sup>2</sup> It seemed important to determine whether shock due to varying types of burns might not similarly result from more than one mechanism, depending upon the characteristics of the burn.

The principal evidence for the view that burn shock may result from local fluid loss is based upon the work of Blalock<sup>1</sup> and Harkins<sup>3</sup> who found by actual measurement that considerable local fluid loss occurs in and near the burned areas. The degree of local fluid loss which they found was considered sufficient to account for some or all of the deleterious effects in early burn shock. The significance of their results will be discussed later.

In the course of extensive investigation on burn shock, we, as well as Elman and Lischer<sup>4</sup> have observed that following a slight burn marked edema occurs, whereas with more severe burns the amount of visible edema appears to be considerably less. As a result of this observation, we decided to investigate the degree of local fluid loss in various types of burns and to determine whether or not there was a correlation between the occurrence of shock and the degree of local fluid loss.

## METHODS

Two types of burns were produced in the following ways: (1) A mild burn involving a small part of the body surface was produced in sixty rats by immersing a single hind limb of the etherized animal up to the hip in water at 75° C. for ten seconds. The area burned was approximately 7 per cent of the body surface as determined by post-mortem dissection. (2) A severe burn involving the same small area was produced by immersing the hind limb of twenty-seven chloroformed rats into boiling water for from two to three minutes.

The animals were not given food or water after the burning procedure.

The fluid shifts in burned animals were evaluated on the basis of bisection studies, using a method previously described by Hechter and co-workers.<sup>5</sup> After determining the body weight, midline skin incisions extending from the head to the tail were made upon the

Aided by grants from the Blanche May Selden Fund, the Martha Kirschner Haft Memorial Fund, F. Brice, and Morton May.

Received for publication, May 4, 1944.

ventral and dorsal surfaces of the animal. The thoracic and abdominal contents were then removed and the carcass weight determined. The lower portion of the body was divided from the upper half by cutting through all of the tissue layers and the spinal column on a line parallel to, and just below, the lowest ribs of the thoracic cage. The vertebral column and the tail were then removed by careful

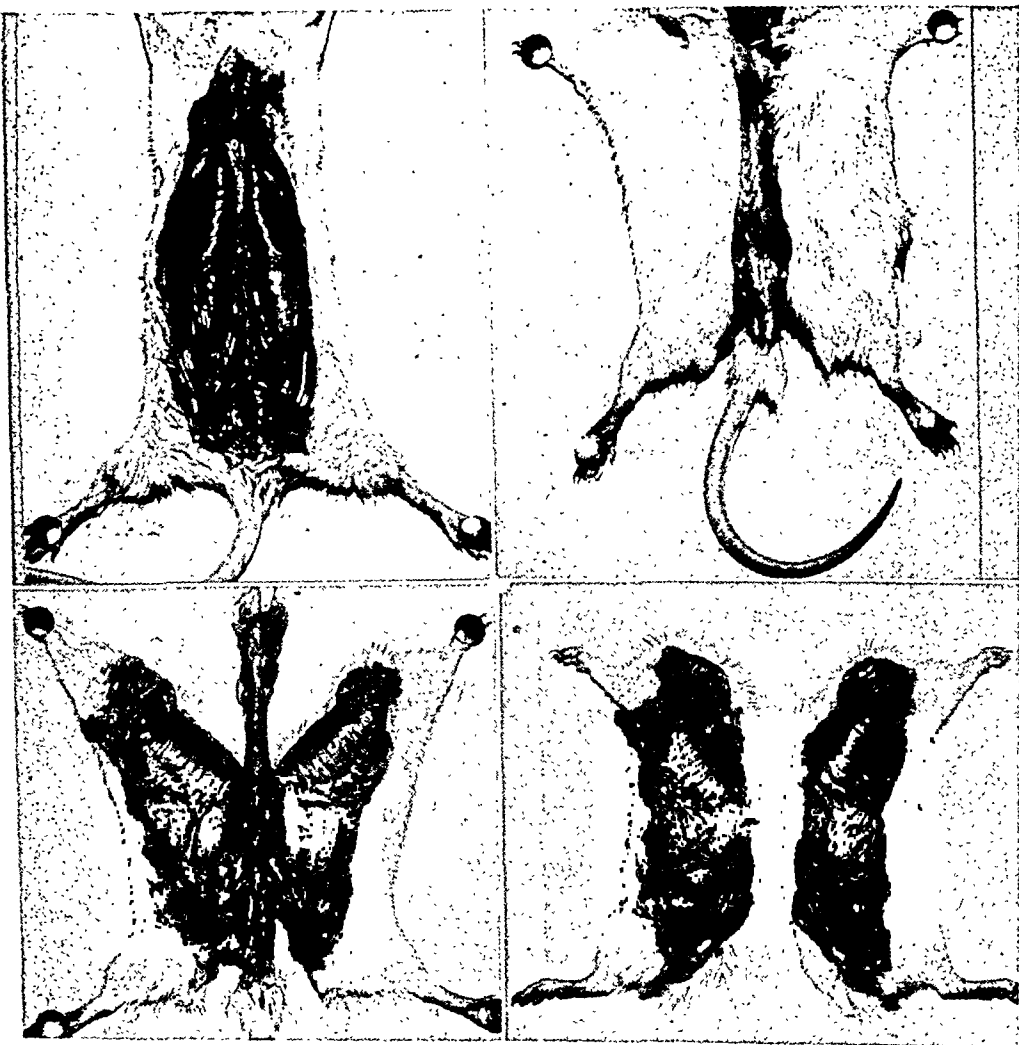


Fig. 1.—Method of bisection. The last step is not shown, which involves separation of the lower quadrants by an incision paralleling the lowest rib.

dissection, thus separating the two lower extremities. By comparing the weight of the burned side with that of the nonburned side of the animal, the degree of fluid shift evaluated as per cent of the body weight was measured (Fig. 1).

The accuracy obtainable with this method of bisection is illustrated in Table I where the results obtained on twelve consecutive measure-



TABLE I

THE VARIATION BETWEEN THE TWO LOWER QUADRANTS OF NONBURNED RATS,  
USING THE BISECTION METHOD

EXP. NO.	RAT BODY WEIGHT (GM.)	RIGHT LEG	LEFT LEG	DIFFERENCE (GM.)	DIFFERENCE AS PER CENT OF BODY WEIGHT
1	240	33.1	32.0	1.1	0.5
2	207	25.0	23.5	1.5	0.7
3	250	33.3	33.7	0.4	0.2
4	240	34.9	33.7	1.2	0.5
5	180	24.4	25.6	1.2	0.8
6	170	24.6	24.8	0.2	0.1
7	164	23.3	23.7	0.4	0.2
8	156	22.0	23.7	1.7	1.1
9	177	26.2	24.8	1.4	0.8
10	138	19.5	20.0	0.5	0.4
11	197	28.2	29.0	0.8	0.4
12	151	22.1	22.3	0.2	0.1

ments on nonburned animals are shown. It will be seen that the difference between the two lower quadrants varied from 0.1 to 1.1 per cent of the body weight (0.2 to 1.7 Gm.), the average being 0.5 per cent. These variations of the method of bisection for rats are in the same range as those reported by Blalock<sup>1</sup> in dogs.

#### RESULTS

*Slight Burn Involving Small Surface of the Body.*—Animals receiving a 75° C. burn for ten seconds involving one limb remained in excellent condition and never went into shock. The limb, and especially the paw, became markedly edematous and on incision exuded fibrinous fluid (Fig. 2). In order to determine how rapid the fluid accumulated, animals were sacrificed one, five, twenty-four and forty hours after this burn. The degree of local fluid loss is shown graphically in Fig. 3. It will be seen that animals lose, on the average, 2 per cent of their body weight into the burned quarter at one hour; 3.3 per cent at five hours; 3.9 per cent at twenty-four hours; and 3.8 per cent at forty hours after thermal injury. It is of importance to observe that seven animals lost 5 per cent or more of their body weight in fluid and yet remained in excellent condition, not developing shock. The results demonstrate three things: First, a slight burn involving a small area of the body surface produces considerable local fluid loss but does not lead to the development of shock; second, most of the local fluid loss with this burn occurs very rapidly, as Harkins<sup>3</sup> has also demonstrated; third, animals can lose over 5 per cent of their body weight locally and do not develop shock if the loss takes place slowly.

*Severe Burn Involving Small Surface.*—The findings with the slight burn are in striking contrast to the results obtained in animals in which a severe burn was produced over the same area of the body surface involving one extremity. It was observed with the 100° C. burn that the burned limb became hard and pale. Visible local edema in the



Fig. 2.—Right hind limb of rat burned at 75° C. for ten seconds showing marked edema of the right limb. Animals with this mild degree of burn do not go into shock.

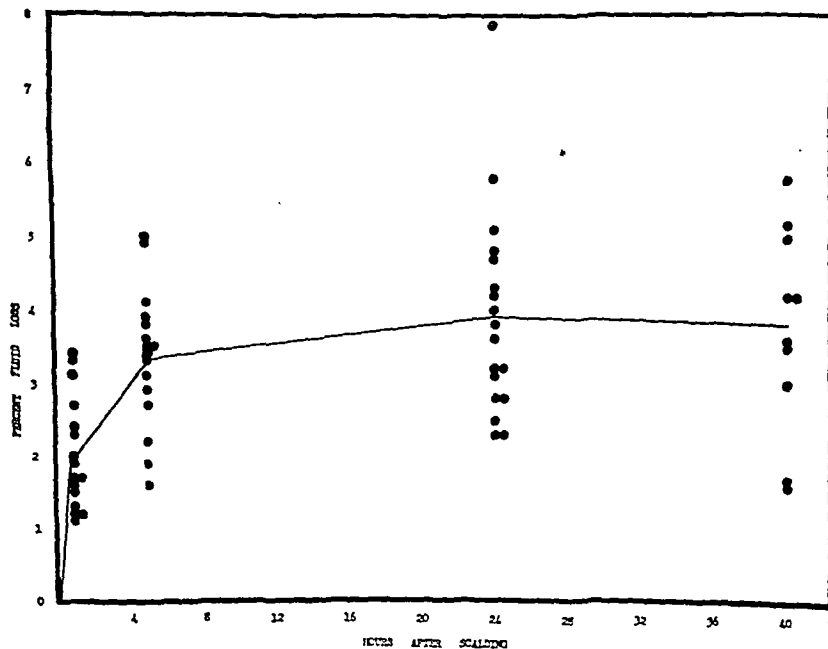


Fig. 3.—Local fluid loss obtained in sixty rats burned at 75° C. for ten seconds on one hind limb. These animals did not go into shock.



Fig. 4.—Right hind limb of rat burned at  $100^{\circ}$  C. for two minutes. The limb is shrunken and does not appear edematous. Animals burned in this manner with little local fluid loss exhibited shock (thirteen of twenty-seven died).

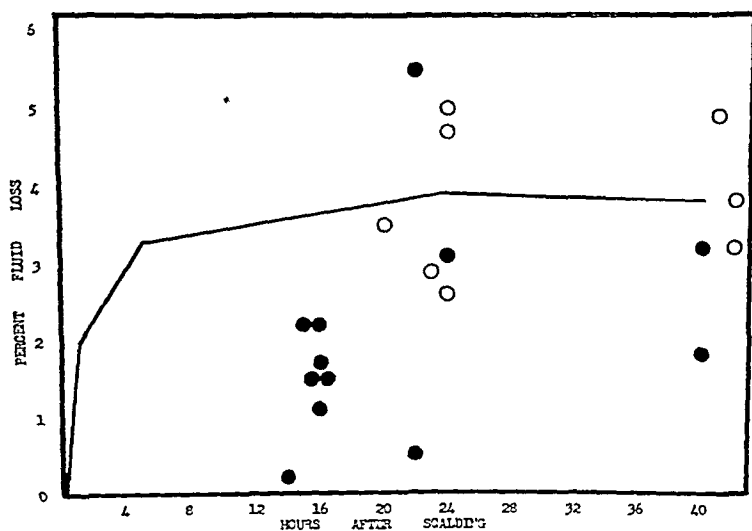


Fig. 5.—Local fluid loss obtained in twenty-six rats following a burn of one hind limb at  $100^{\circ}$  C. for from two to three minutes. The dots represent animals that died in shock. The circles represent animals that were killed at the times shown. The curve is the average fluid loss represented in Fig. 3, demonstrating the degree of fluid loss of animals not going into shock. Eleven of the twelve animals that died had less fluid loss than was found in mildly burned animals not going into shock.

TABLE 11

THE FLUID SHIFT INTO A HIND LIMB BURNED AT 100° C. FOR FROM TWO TO THREE MINUTES

TIME OF DEATH OR KILLING AFTER BURN (HR.)	DIED OR KILLED	RAT BODY WEIGHT	NORMAL LEG WEIGHT	BURNED LEG WEIGHT	DIFFER- ENCE IN WEIGHT (GM.)	DIFFER- ENCE AS PER CENT OF BODY WEIGHT
14	Died	193	34.7	35.2	0.5	0.2
16	Died	326	53.1	60.4	7.3	2.2
16	Died	176	37.6	40.5	2.9	1.7
16	Died	207	39.7	42.9	3.2	1.5
16	Died	162	25.0	27.4	2.4	1.5
16	Died	200	35.7	37.9	2.2	1.1
16	Died	175	30.5	34.3	3.8	2.2
22	Died	166	29.8	30.6	0.8	0.5
22	Died	236	41.0	55.0	14.0	5.5
24	Died	170	27.3	32.6	5.3	3.1
40	Died	185	32.6	38.6	6.0	3.2
40	Died	183	31.1	34.4	3.3	1.8
20	Killed	163	27.5	33.2	5.7	3.5
23	Killed	166	28.1	33.0	4.9	2.9
24	Killed	149	23.0	30.0	7.0	4.7
24	Killed	368	54.2	72.7	18.5	5.0
24	Killed	195	35.3	40.3	5.0	2.6
47	Killed	180	28.8	34.5	5.7	3.2
48	Killed	171	30.0	36.5	6.5	3.8
43	Killed	199	31.0	40.9	9.9	4.9

burned extremity was not evident (Fig. 4). These animals appeared to be in shock and 13 of 27 died within forty hours. The average local fluid loss of 12 of these animals (excluding one because the burned limb was chewed off) was 2.05 per cent of the body weight. The degree of local fluid loss was greater in the 14 animals that did not die but were sacrificed after forty hours than in those that died in shock, the average being 3.7 per cent (Fig. 5 and Table II).

These results demonstrate that severely burned animals die in shock with less local fluid loss than that observed in slightly burned animals not going into shock. Similarly, in the second experiment, the animals that died following a severe burn exhibited less local fluid loss than those surviving the same burn.

#### DISCUSSION

Blalock<sup>1</sup> and Harkins<sup>3</sup> have shown that fluid loss in and near the burned area is an important factor in the development of burn shock. In this report, it has been clearly demonstrated that animals may die in shock with insignificant local fluid loss following a severe burn. It has been shown that animals mildly burned, not developing shock, exhibit greater local fluid loss than the animals dying from severe burns. Similarly it has been shown that the animals which survived the severe burn exhibited considerably greater local fluid loss than those rats which succumbed. It is therefore apparent that following certain types of burns, animals may die in shock not due to local fluid loss. We have also found in studying 64 animals that were burned

(over 30 to 39 per cent of their body surfaces for ten seconds at 100° C.) that death may occur with insufficient local fluid loss.

The mechanism of death of those animals dying without significant local fluid loss is unknown. It would be useless to speculate on the importance of neurogenic or toxic factors without further evidence. The finding of little local fluid loss does not indicate that the effective circulating blood volume in these animals was not reduced. We are now studying this problem.

In view of our results it would appear probable that Blalock<sup>1</sup> and Harkins<sup>3</sup> might have obtained considerably greater fluid loss with less shock by employing a smaller degree of burn, since the burns they employed were more severe than those used in our experiments where little fluid loss was encountered. It is of interest to observe that Harkins, who used a Bunsen burner for ten minutes, observed less fluid loss than did Blalock, who presumably obtained a lesser degree of thermal injury with hot irons.

It is apparent that in view of these results, therapeutic measures successful in the treatment of one type of burn shock are not necessarily effective in other types. For the past three years we have intensively studied the burn shock which results from scalding 80 to 90 per cent of the body surface of rats and mice for ten seconds at 65 or 75° C.<sup>6</sup> It appears likely that the shock produced by this method is due in large part, at least, to local fluid loss, since we have shown in this study the large amount of fluid which can accumulate into a single limb burned in this manner. If shock from burns is ever due to local fluid loss alone, it should occur under these circumstances, which are more favorable for the production of local fluid loss than any others with which we are acquainted. This might be the explanation for the unusual results originally found by Rosenthal<sup>7</sup> and confirmed by us,<sup>8</sup> that the therapeutic effect of plasma could be accounted for entirely by its sodium content. It has been recently shown by Fox<sup>9</sup> that the amount of sodium in a mildly burned area is disproportionately high, and it is thought that the depletion of sodium from the rest of the body may be an important factor in the development of shock. This offers an explanation for the therapeutic effect of sodium salts in the type of shock found in widespread mild burns. It would appear probable that the sodium factor is less important in shock due to severe burns with insignificant local fluid loss, because it seems likely that the characteristics of the burn which reduce fluid loss would be expected to reduce sodium loss as well. Thus, it is possible that plasma may prove to be superior to saline solution in the type of burn shock with insufficient local fluid loss, as it is in the case in other types of traumatic shock. Likewise, agents effective in the shock due to local fluid loss may be ineffective in the other type of burn shock. Thus, liver extract<sup>6</sup> and sodium salts<sup>7</sup> effective in one type may not be effective in the second type.

It is extremely likely that in clinical burns both factors are of importance and may operate simultaneously in varying degrees. In more severe burns the factor of local fluid loss would appear to be less important, whereas with more widespread mild burns, which produce marked edema and weeping of the skin, the local fluid loss factor may play a greater role. It might be pointed out that patients with widespread severe sunburn with a great deal of local swelling do not as a rule go into shock. Considering the results obtained in this study, it appears to us that the role of local fluid loss in clinical shock from burns may have been overemphasized.

We do not mean to imply from this study that there are only two types of burn shock. It is possible and extremely probable that other factors as yet unknown are implicated. In fact, it is possible that the second "type" without local fluid loss is due to more than one mechanism. The pathogenesis of this type of shock is now being investigated.

#### CONCLUSIONS

1. Rats who were mildly burned at 75° C. for ten seconds on a single hind limb developed marked visible edema with considerable local fluid loss but did not develop shock.

2. Rats whose single hind limbs were severely burned at 100° C. for from two to three minutes died in shock without visible edema and exhibited insufficient local fluid loss to account for death. Similar results have been obtained when larger areas of the body were severely burned for ten seconds.

3. It is therefore apparent that there are at least two mechanisms capable of producing shock: one due to local fluid loss and the other due to some unknown factor(s).

4. This difference in the mechanism of production of burn shock may explain some of the differences of opinion regarding therapeutic agents in burns.

#### REFERENCES

1. Blalock, A.: *Principles of Surgical Care: Shock and Other Problems*, St. Louis, 1940, The C. V. Mosby Co.
2. Prinzmetal, M., Freed, S. C., and Kruger, E.: *The Pathogenesis and Treatment of Shock Resulting From Crushing of Muscle*, *War Med.* 5: 74, 1944.
3. Harkins, H. N.: *The Treatment of Burns*, Springfield, Ill., 1942, Charles C Thomas.
4. Elman, R., and Lischer, C.: *Local Skin Lesion in Experimental Burns and Its Relation to Systemic Manifestations*, *Surg., Gynec. & Obst.* 78: 346, 1944.
5. Hechter, O., Krohn, L., and Harris, J.: *Role of Adrenals in Production of Traumatic Shock in Rats*, *Endocrinology* 31: 439, 1942.
6. Prinzmetal, M., Hechter, O., Margoles, C., and Feigen, G.: *A Principle From Liver Effective Against Shock Due to Burns*, *J. A. M. A.* 122: 720, 1943.
7. Rosenthal, S. M.: *Experimental Chemotherapy of Burns and Shock. Effects of Systemic Therapy on Early Mortality*, *Pub. Health Rep.* 58: 513, 1943.
8. Prinzmetal, M., Bergman, H. C., and Hechter, O.: *In preparation*.
9. Fox, C. L., Jr.: *Personal communication*.

## FURTHER STUDIES ON THE ROLE OF BACTERIA IN SHOCK DUE TO CRUSHED MUSCLE IN DOGS\*

S. C. FREED, M.D., H. E. KRUGER, AND MYRON PRINZMETAL, M.D.

SAN FRANCISCO, CALIF.

(From the Harold Brunn Institute, Mount Zion Hospital)

IN A recent publication from this laboratory,<sup>1</sup> a technique was reported by which shock could be regularly produced in dogs by crushing a known amount of muscle with minimal loss of blood. It was shown that the shock thus produced was a direct result of bacterial action. For it was observed that despite strict, aseptic surgical technique, the crushed muscle was always grossly contaminated. If, however, the bacteria were inhibited by the use of antibacterial agents, shock did not occur and all animals remained in excellent clinical condition. In these experiments sulfamerazine was administered both locally and systemically. In addition, in one group of animals the crushed muscle was soaked in acriflavine solution as was first performed by Abraham and his associates,<sup>2</sup> with intraperitoneal implantation of liver tissue. Untreated animals were obviously in shock at the end of twenty-four hours, there was a decrease in circulating blood volume, the limb operated upon was decidedly swollen, the crushed muscle at autopsy always had a foul odor, gas was often present, and direct smear of the muscle revealed numerous bacteria of many types. This was in striking contrast to the treated animals in which a decrease in blood volume was infrequent, less swelling of the operated quarter was observed, and the crushed muscle at autopsy appeared clean, had no odor, and revealed few or no organisms in direct smear. Despite the considerable swelling of the leg in the untreated animals, it was demonstrated that the local fluid loss was insufficient to account for the shocklike state, and it was concluded that this was an example of toxic shock, as distinguished from extravasative shock induced by other methods such as blows or certain types of burns.

In the first report,<sup>1</sup> it was shown that the systemic administration of sulfamerazine immediately after trauma prevented the occurrence of shock. The following problems seemed of practical importance: How late can the sulfamerazine be administered and still be effective? When administered systemically, does the sulfamerazine penetrate into the ischemic, crushed muscle and in what concentration? What is the relative efficiency of local as compared with systemic administration of the drug?

\*Aided by a grant from Columbia Foundation for Medical Research.  
Received for publication, June 10, 1944.

*Experiment 1. The Local Application of Sulfamerazine.*—In eleven dogs the sulfamerazine was administered locally in the following manner. The drug was thoroughly mixed with the crushed muscle before reinsertion. The dosage was 0.5 Gm. of sodium sulfamerazine per 10 Gm. of muscle. No other treatment was given. Nine dogs remained in excellent condition and only two went into shock and died. There was no decrease in blood volume in the animals not going into shock.

It should be emphasized that, in this experiment, the animals received only one administration of the drug and were given no additional therapy. The blood concentration of sulfamerazine was very low (2.5 to 3.5 mg. per cent) and at times only a trace was found.

It appears that the local administration of sodium sulfamerazine was moderately beneficial since shock did not occur in nine out of eleven animals. It is, therefore, apparent that local treatment alone may not be completely effective.

*Experiment 2. The Systemic Administration of Sulfamerazine Six Hours After Trauma.*—Ten dogs received sodium sulfamerazine (0.2 Gm. per kilogram body weight) intravenously six hours after reinsertion of the crushed muscle. Subsequent daily doses (0.1 Gm. per kilogram body weight) were given orally. The average sulfamerazine blood level of these ten animals was 15.2 mg. per cent, ranging from 9.2 to 20.8 mg. per cent. All ten animals remained in good condition and in seven of the dogs there was no significant change in circulating blood volume (Table I). The wounds of these animals at autopsy appeared clean and had no odor. Cultures of the crushed muscle were sterile in

TABLE I

EFFECT ON BLOOD VOLUME OF CRUSHED MUSCLE OF DOGS RECEIVING SULFAMERAZINE SIX HOURS AFTER TRAUMA

DOG NO.	WEIGHT (KG.)	WT. OF CRUSHED MUSCLE (GM.)	TIME (HR.)	HEMATO-CRIT (%) R.B.C.)	PLASMA VOLUME (C.C.)	BLOOD VOLUME (C.C.)	OUTCOME
1	6.8	34.6	0	---	463.0	---	No shock
			24	46.0	429.0	794.0	
2	8.2	34.7	0	33.5	424.0	638.0	No shock
			24	34.5	428.0	652.0	
3	5.9	35.7	0	---	397.0	---	No shock
			24	30.5	293.0	422.0	
4	5.4	17.7	0	30.0	477.0	681.0	No shock
			24	31.5	458.0	669.0	
5	12.8	53.4	0	40.0	467.0	778.0	No shock
			24	35.5	514.0	796.3	
6	10.9	51.3	0	36.0	639.0	997.0	No shock
			24	38.0	546.0	880.0	
7	9.5	49.3	0	36.0	477.0	746.0	No shock
			24	37.5	560.0	896.0	
8	6.8	30.0	0	38.0	364.0	587.0	No shock
			24	35.5	377.0	585.0	
9	10.0	40.0	0	32.0	816.0	1200.0	No shock
			24	44.5	440.0	794.0	
10	9.1	37.5	0	35.5	482.0	748.0	No shock
			24	38.0	257.0	415.0	



three, in the remainder the muscle was contaminated but had fewer organisms than the crushed muscles of untreated animals.

It is concluded that the systemic administration of sulfamerazine in adequate doses is completely successful in preventing shock when administered six hours after trauma.

*Experiment 3. The Systemic Administration of Sulfamerazine Seventeen Hours After Trauma.*—Ten dogs received sodium sulfamerazine (0.2 Gm. per kilogram body weight) intravenously sixteen to eighteen hours after reinsertion of the crushed muscle. Subsequent daily doses (0.1 Gm. per kilogram body weight) were given orally. The average sulfamerazine blood level of these animals was 10.0 mg. per cent, with a range of from 7.4 to 13.2 mg. per cent. Shock developed in five of the dogs, three of which died within seventy-two hours. The reductions in blood volume of these animals are recorded in Table II. The wounds of all of these dogs had an unpleasant odor and culture of the muscle at autopsy revealed contamination.

TABLE II

EFFECT ON BLOOD VOLUME OF CRUSHED MUSCLE OF DOGS RECEIVING SULFAMERAZINE SEVENTEEN HOURS AFTER TRAUMA

DOG NO.	WEIGHT (KG.)	WT. OF CRUSHED MUSCLE (GM.)	TIME (HR.)	HEMATO-CRIT (% R.B.C.)	PLASMA VOLUME (C.C.)	BLOOD VOLUME (C.C.)	OUTCOME
1	11.8	60.3	0	39.0	840.0	1377.0	Died 24 hr.
			24	---	---	---	
2	9.5	50.5	0	37.0	570.0	840.0	Shock but
			24	38.0	---	---	recovered
3	8.6	61.1	0	36.0	559.0	872.0	Shock but
			24	32.0	380.0	560.0	recovered
4	7.3	39.0	0	30.0	361.0	515.0	Died 24 hr.
			24	---	---	---	
5	5.5	23.4	0	27.0	387.0	545.0	No shock
			24	27.0	386.0	544.0	
6	9.1	43.2	0	35.0	377.0	580.0	Died 36 hr.
			24	40.0	357.0	595.0	
7	10.5	62.1	0	40.5	573.0	964.0	Shock but
			24	42.0	536.0	924.0	recovered
8	8.6	25.5	0	28.0	840.0	1166.0	No shock
			24	25.0	672.0	866.0	
9	9.1	60.0	0	36.5	622.0	980.0	No shock
			24	32.0	318.0	468.0	
10	9.1	57.0	0	34.0	662.0	1003.0	No shock
			24	35.5	434.0	670.0	

It would seem that sulfamerazine therapy is only of moderate benefit when given as late as seventeen hours after injury.

*Experiment 4. The Systemic Administration of Sulfamerazine Twenty-four to Twenty-six Hours After Trauma.*—Eleven dogs received sulfamerazine therapy as described, the initial dose being given intravenously twenty-four to twenty-six hours postoperatively. All eleven of these animals went into shock and five died. At autopsy, the wounds of

these animals had a foul odor and cultures revealed heavy bacterial growth.

It should be mentioned that all animals were in shock at the end of twenty-four hours when sulfamerazine therapy was begun. It, therefore, appears clear that sulfamerazine has no therapeutic effect when administered twenty-four hours after trauma.

*Experiment 5. Concentration of Sulfamerazine in Blood and Tissues of Dogs Subjected to Muscle Crushing.*—Determinations of sulfamerazine were done in the blood, the crushed muscle, and the normal muscle of animals in the preceding experiments.

In Experiment 1, when the drug was administered locally only, the blood concentration twenty-four hours later was between 2.5 and 3.5 mg. per cent; four days later at autopsy only a trace was found in the blood and the normal muscle, while the crushed muscle contained between 1,000 and 2,000 mg. per 100 Gm. of dry tissue.

In animals treated by the systemic administration of sulfamerazine in this and the previous report, it was found that the average blood level of twenty-two dogs was 11.6 mg. per cent with a range of from 6.3 to 20.8 mg. per cent. In twenty-two out of twenty-four instances the concentration of the sulfamerazine in the crushed muscle was higher than that in the normal muscle of the same animal. The average concentration in crushed muscle of twenty-four animals was 62.1 mg. per cent with a range of from 14.3 to 161.5 mg. per cent. The average concentration in the normal muscle of twenty-two dogs was 23.5 mg. per cent with a range of from 5.5 to 38.5 mg. per cent (Table III).

It is of interest that following systemic administration of sulfamerazine, the ischemic, traumatized tissue contains considerably higher concentration in the normal muscle of twenty-two dogs was 23.5 mg. This fact, the explanation of which is not entirely understood, would appear to be significant because the drug accumulates in high concentration in areas where it is most needed in spite of such areas being unconnected with the systemic circulation.

#### DISCUSSION

An attempt was made to determine: (1) How long after trauma the administration of sulfamerazine is effective in the prevention or treatment of toxic shock in dogs, and (2) the most appropriate method of administration.

It was found that the local application of this drug without subsequent systemic administration might be effective but is not completely so because an adequate blood concentration is not maintained. The systemic administration of sulfamerazine was found to be the most effective. In the previous study it was shown that this drug completely prevents shock when administered immediately after trauma. In the

present study, it was demonstrated that therapy may be begun six hours after trauma and, with the establishment and maintenance of a high blood level of the drug, shock is completely prevented. If a delay of seventeen hours takes place before sulfamerazine is given, the onset of shock is not prevented but its further development may be arrested, and it would seem that the drug may be of some benefit when administration is begun after seventeen hours. Sulfamerazine therapy, if begun later than twenty-four hours after trauma, seems to be ineffective even though a high blood level is established. It is interesting to note that this time relationship holds true for the débridement experiments reported in our previous study.<sup>1</sup> In the animals treated with sulfamerazine twenty-four hours after trauma, shock was well advanced and the dogs died shortly thereafter. It is possible that if these animals could be brought out of shock by the use of plasma, allowing them to live longer, the sulfamerazine might prove to be more effective.

Whether or not this time relationship between trauma and effectiveness of therapy holds true for human beings is not known. However, it is obviously important that patients with injuries that cause marked crushing of tissues should receive intensive antibacterial therapy as

TABLE III  
CONCENTRATION OF SULFAMERAZINE IN BLOOD AND TISSUES OF DOGS  
WITH CRUSHED MUSCLE

EXPERIMENT	DOG NO.	BLOOD (MG. %)	NORMAL MUSCLE (MG. %)*	CRUSHED MUSCLE (MG. %)
Systemic administration of sulfamerazine immediately after trauma	1	14.3	Trace	23.0
	2	6.5	5.5	14.3
	3	6.3	8.7	11.8
	4	---	26.9	29.4
	5	7.9	17.0	58.1
	6	12.3	31.3	50.0
	7	11.7	16.3	65.8
	8	12.5	15.6	107.6
	9	11.6	17.0	113.0
	10	11.6	15.5	48.0
	11	11.6	38.5	65.8
Mean		9.5	17.5	53.1
Systemic administration of sulfamerazine six hours after trauma	12	13.5	29.4	61.0
	13	15.6	20.2	---
	14	14.3	11.5	100.0
	15	16.7	27.3	161.5
	16	13.2	24.5	17.5
	17	18.6	28.5	57.6
	18	9.2	15.5	---
	19	20.8	40.0	105.5
Mean		15.2	24.6	83.9
Systemic administration of sulfamerazine seventeen hours after trauma	20	8.5	12.5	39.7
	21	13.2	25.0	55.0
	22	10.8	40.0	25.0
	23	7.4	17.0	48.0
	24	---	47.5	78.4
Mean		10.0	28.4	49.2
Total Mean		11.6	23.3	62.1

\*Mg. per 100 Gm. dry tissue.

soon as possible. Even though, in our experiment, sulfamerazine proved to be ineffective when administration was delayed for twenty-four hours, nevertheless, the drug should be administered to patients for some possible benefit. In these cases, the use of plasma would appear to be most important since, if the shock can be controlled with plasma, the antibacterial agents may now be effective. It is clear that local

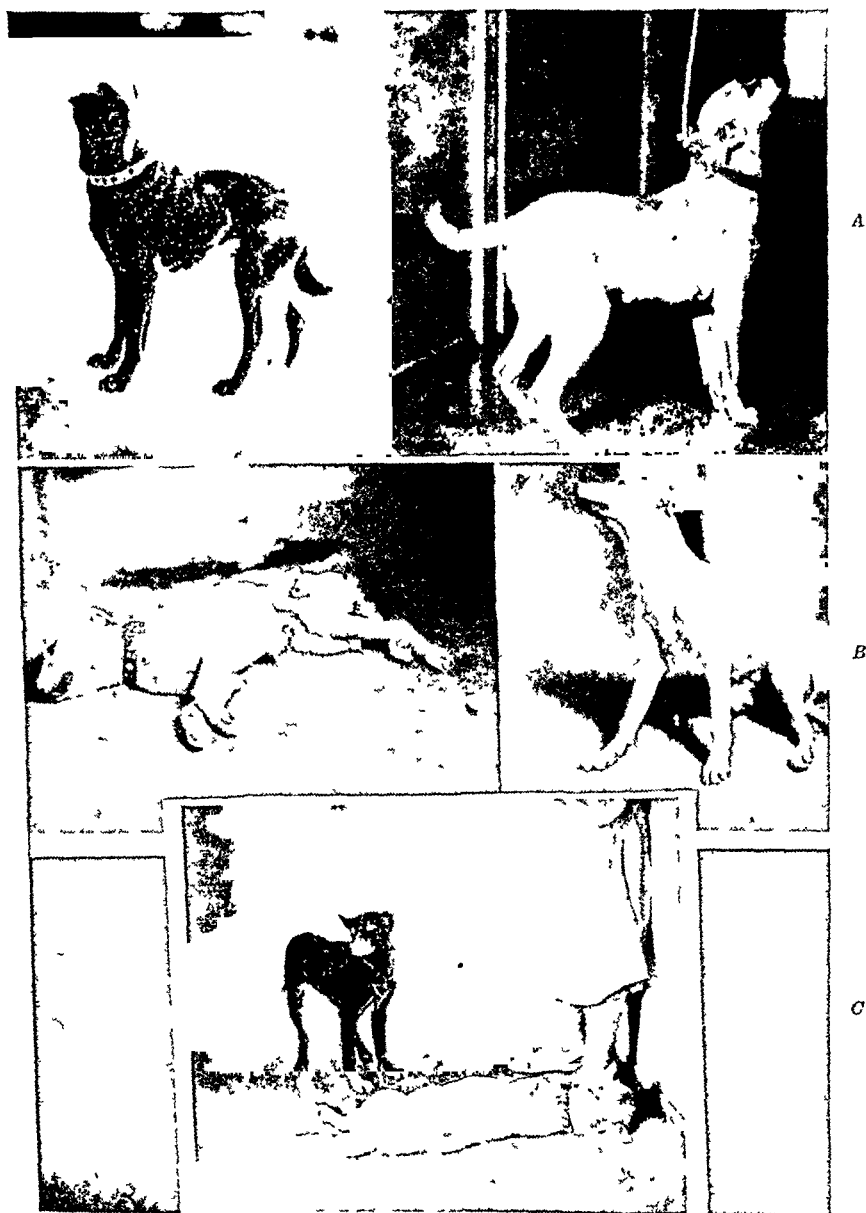


FIG 1—Two dogs (A) before being subjected to muscle-crushing procedure, and (B) twenty-four hours after operation, one dog received sulfamerazine therapy and is in good condition the other dog received no treatment and is in profound shock (C) Four days after operation, dog which received sulfamerazine is in good condition, and dog which remained untreated is dead.

administration of the drug, while of great benefit, may be insufficient to prevent shock and death, and systemic administration should be employed.

Treatment of toxic shock due to this type of muscle crushing with antibacterial agents continues to be extremely satisfactory. Re-emphasizing the role of bacteria in toxic shock, it is of interest to note that, so far, of fifty dogs which received adequate antibacterial treatment in this and the previous study, none developed shock and all remained in excellent clinical condition, whereas of fifty-two untreated or inadequately treated dogs, fifty developed severe shock and the majority died.

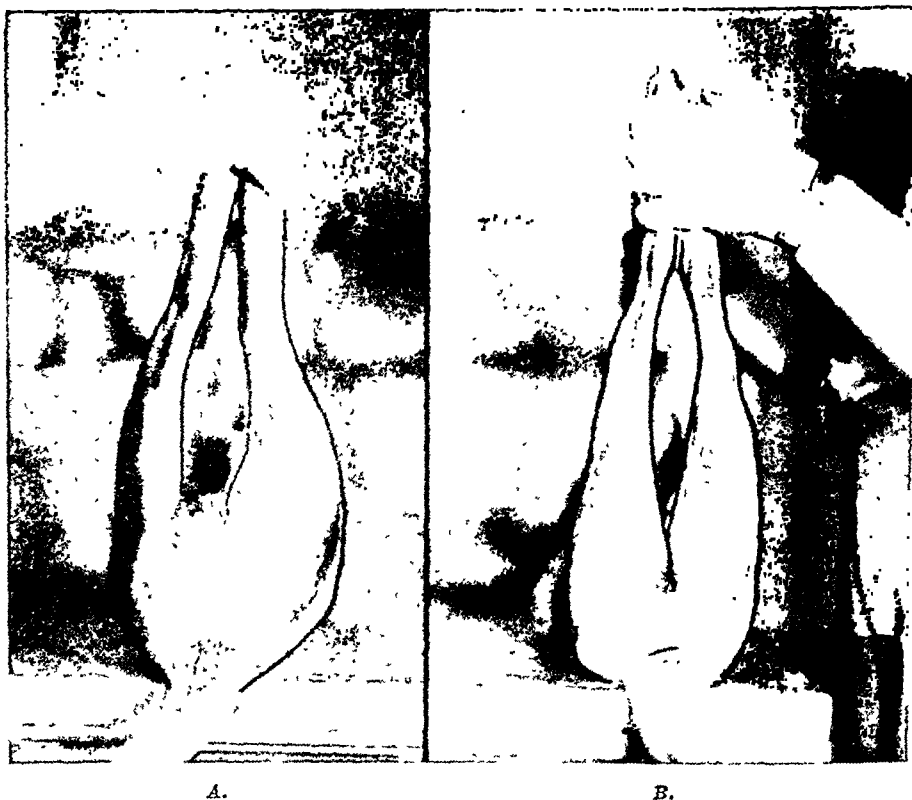


Fig. 2.—Hindquarters of both animals, demonstrating the difference in size of operated legs. Treated dog (B) has only very slight swelling of operated leg. Untreated dog (A) has decided swelling of operated quarter, a great deal of which is due to gas.

We wish to mention here that, to us, the clinical appearance of the animals has proved to be the most important diagnostic factor in this type of shock. Fig. 1 shows two dogs (A) before being subjected to the muscle crushing procedure, (B) twenty-four hours after the operation, and (C) on the fourth day after operation. One dog received sulfamerazine therapy and the other dog was untreated. The treated dog remained in good condition except for a slight limp when walking. The untreated animal was in shock twenty-four hours after the operation and was dead on the fourth day. Fig. 2 shows the difference in

size of the operated legs of the two animals. The leg of the treated dog is only slightly swollen and the operated leg of the untreated dog is decidedly swollen, due mainly to gas with a moderate amount of fluid. Fig. 3 shows the wounds of the two animals at autopsy. The wound of the treated dog appears relatively clean and dry although



B

Fig 3—Wounds of the two animals at autopsy. A, Wound of animal treated with sulfamerazine appears relatively clean and dry. B, Wound of untreated animal shows accumulation of fluid.

the crushed, devitalized muscle is present in large amounts (79.0 Gm. of muscle was crushed in this case, 0.65 per cent of the body weight). The wound of the untreated animal shows the amount of fluid present. The weight of the muscle crushed in this case was 56.0 Gm., 0.41 per cent of the body weight.

The local and systemic use of penicillin in the muscle-crushing type of shock is being investigated at the present time, and the use of sulfamerazine in other types of shock will be presented in future reports. The treatment of animals in shock twenty-four hours after trauma is also being investigated.

#### CONCLUSIONS

1. Sulfamerazine administered locally partially prevents shock induced by muscle crushing.

2. Systemic administration of sulfamerazine immediately or six hours after operation is completely effective in preventing the occurrence of this type of shock.

3. Systemic administration of sulfamerazine seventeen hours after operation is slightly effective.

4. Systemic administration of sulfamerazine twenty-four hours after operation is ineffective.

5. After systemic administration of sulfamerazine, the ischemic, crushed tissue contains a higher concentration than does the normal muscle of the same animal.

6. If these results are applicable to human beings with crush injuries, treatment should be as follows: Following débridement, sulfamerazine should be administered both locally and systemically and the drug continued for several days in adequate amounts.

7. The role of bacteria in shock due to muscle crushing is re-emphasized, for fifty out of fifty-two untreated or inadequately treated animals developed shock and the majority died, whereas none of fifty dogs adequately treated by antibacterial agents developed shock.

#### REFERENCES

1. Prinzmetal, M., Freed, S. C., and Kruger, H. E.: Pathogenesis and Treatment of Shock Resulting from Crushing of Muscle, *War Med.* 5: 74, 1944.
2. Abraham, E. P., Brown, G. M., Chain, E., Florey, H. W., Gardner, A. D., and Saunders, A. G.: Tissue Autolysis and Shock, *Quart. J. Exper. Physiol.* 31: 79, 1941.

# THE RETENTION OF INTRAVENOUSLY INFUSED GELATIN

## OBSERVATIONS IN MAN<sup>\*</sup>

ALEXANDER BRUNTSCHWIG, M.D., AND SABRA NICHOLS, B.S., CHICAGO, ILL.

*(From the Department of Surgery, University of Chicago)*

IN RECENT years parenteral injection of nitrogenous nutriment has become feasible by virtue of the development of casein digests suitable for intravenous injection. Evidence has also been presented in support of the view that protein molecules injected intravenously (homologous plasma proteins) might be utilized for nutrition. The use of "complete" foreign proteins would not seem possible in view of their antigenic properties. However, certain samples of gelatin have recently been found suitable for intravenous injection in that no immediate reactions were produced (except in isolated instances and these were not serious), sensitization did not develop, and no late toxic effects were manifested.<sup>1, 2</sup> Gelatin, however, is an incomplete protein in that it lacks a number of the essential amino acids. As the sole source of protein in the diet, it will not permit of normal growth and development of experimental animals.

In view of the tolerance of human patients to repeated intravenous injections of gelatin, and evidence that some of it is metabolized,<sup>2</sup> further studies were carried out in a series of twenty-three patients to determine how much of this material might be excreted in the urine under the usual conditions of intravenous clinical administration. This question is of obvious importance since if most of the injected material is excreted unchanged in the urine, little opportunity for utilization will be afforded and further investigations of gelatin (and possibly other nonantigenic foreign proteins) as an intravenous nutriment will hardly be worth while.

### METHODS

Twenty-three patients with various conditions received one or repeated daily intravenous injections of gelatin. In some instances the injections were made in the immediate postoperative period, and the studies carried out when the patient was receiving almost nothing by mouth. In others, the studies were carried out while the patient was partaking of the usual hospital diet. Where one injection was given urine was collected for at least seven days including, of course, the day of injection. Furthermore, urine was collected prior to injection for the control studies which will be discussed. Where several consecutive daily injections were given, urine was collected after cessation of injections until no gelatin could be detected in them.

<sup>\*</sup>This study was facilitated by a grant from the Edible Gelatin Manufacturers Research Society, New York, N. Y.

Received for publication, May 17, 1944.



or less there were three who excreted the total amount injected. Each of these exhibited a pyrogenic reaction following the injection and one of the patients had cirrhosis of the liver (Case 17). Of the three who retained small quantities, two had liver disease. It is suggested, therefore, that in primary liver disease there is limited retention of injected gelatin. This might well be anticipated in view of the important role of the liver in protein metabolism. However, in other instances not reported in this study, primary liver disease was sometimes present when there was appreciable retention of injected gelatin.

In Table II are summarized the results in six patients who received several consecutive daily injections. There was appreciable retention in all of them, the average being 40.9 per cent of the gelatin injected. This agrees quite well with the results obtained in studies of single injections where, as stated previously, 43.1 per cent was retained.

TABLE II  
PATIENTS WHO RECEIVED SEVERAL DAILY INJECTIONS

PATIENT	DIAGNOSIS	NO. OF DAILY IN- JECTIONS	GM. OF GELATIN INJECTED	NO. OF DAYS URINE COL- LECTED	GM. OF GELATIN EXCRETED	% OF GELATIN "RE- TAINED"
18. Got.	Carcinomatosis	5	130	13	86.9	33.0
19. Is.	Empyema	8	170.6	14	120.6	28.4
20. Tr.	Carcinoma of colon	5	150	11	86.6	42.4
21. Ha.	Cholecystitis	4	231.7	10	125.8	45.0
22. Di.	Carcinomatosis	8	524.5	10	245.3	53.0
23. Po.	Peptic ulcer	2	130.7	4	74.5	43.0
Average % retained						40.9+

It is not to be inferred that these studies are regarded as final evidence to justify assumption that intravenous gelatin is a protein food. Evidence for appreciable *utilization* is not yet presented. Emphasis is here placed only on the fact that protein as gelatin may be administered to the organism and that there is retention of appreciable quantities of this substance.

#### SUMMARY

Evidence is presented to indicate that 40 to 43 per cent of gelatin injected intravenously in man as an 8 per cent solution in physiologic saline is retained in that only 60 to 57 per cent is recovered in the urine. The relative amount of gelatin retained is approximately the same whether one or eight daily injections are made. Thus, gelatin injected intravenously constitutes one method by which nitrogenous material may be administered to the organism.

#### REFERENCES

1. Brunswick, A., Scott, V. B., Corbin, N., and Moe, R.: *Proc. Soc. Exper. Biol. & Med.* 52: 46-48, 1943.
2. Brunswick, A., Corbin, N., and Johnston, C. D.: *Ann. Surg.* 118: 1058-1063, 1943.

## INTESTINAL OBSTRUCTION

### I. THE PROTECTIVE ACTION OF SUCCINYLSULFATHIAZOLE FOLLOWING SIMPLE VENOUS OCCLUSION\*

STANLEY J. SARNOFF, M.D.,† AND EDGAR J. POTH, M.D., PH.D.,  
GALVESTON, TEXAS

*(From the Departments of Surgery, The Johns Hopkins University School of  
Medicine and The University of Texas Medical Branch)*

THE problem of intestinal obstructions is an extremely complicated one with a large number of variables which cannot be easily controlled even in carefully planned experiments. The importance of the effects of pressure within the lumen of the bowel, and the blood supply to the involved segment, as well as the types and virulence of organisms which are contained in the gut has long been recognized. It would, therefore, be highly desirable in an experimental study if these various factors could be separated and their individual effects evaluated.

Succinylsulfathiazole<sup>1-4</sup> has been shown to alter the bacterial flora of the intestinal tract in a significant manner both in dogs and human beings. It would be interesting, therefore, to observe whether or not an alteration of the bacterial flora would in any manner change the course following venous occlusion of a segment of bowel.

For the purposes of this experiment, a preparation was made which, while seldom reproduced clinically, is so simplified that it is hoped some of the complicating variables will be eliminated. Simple, complete venous occlusion to a segment of bowel without obstruction of the lumen of the bowel was chosen as the preparation for study. This was accomplished by carefully isolating and doubly ligating all of the veins in the mesentery about halfway between the bowel and the root of the mesentery. Care was taken not to injure the accompanying arteries. At either end of the selected segment the arteries and veins in the mesentery running parallel to the axis of the bowel were carefully isolated, doubly clamped, divided, and ligated. The avascular portion of the mesentery at these points was likewise divided, well down toward the root of the mesentery. When this procedure was carried out on a segment of ileum 50 cm. in length lying immediately proximal to the termination of the antimesentery artery of the terminal ileum, no animals survived more than forty-five hours (see Table I).

\*Supported by a grant from Sharp & Dohme, Philadelphia, Pa.

†Fellow in the Department of Surgery, the Johns Hopkins University School of Medicine.

Received for publication, May 8, 1944.

A loop of bowel so treated becomes cyanotic to assume a deep purplish discoloration within thirty minutes. The veins are markedly engorged and the arterial pulsations, which are vigorous at first, become progressively less and finally disappear. The engorged segment of bowel becomes thickened and there is some bleeding into the lumen of the bowel. Beginning at the mesenteric border of the bowel and dissecting downward along the occluded veins to the level of the ligatures, there is extravasation of blood into the mesentery, first noticeable about twenty minutes after the ligatures are applied. Proximal to this point the tissues are normal (Fig. 1). If the segment is exposed to the air, its temperature will have declined to within one degree of the temperature of the room within two and one-half hours.



Fig. 1—A loop of ileum 50 cm. in length is shown twenty minutes after ligation of the veins in the mesentery as well as the artery and vein which run parallel to the axis of the bowel at either end of the segment as indicated by the arrows. The ligatures have been cut long and can be identified. The segment of ileum has become cyanotic and suffused with blood. The veins are distended. The extravasation of blood into the involved mesentery has progressed sufficiently to be visible.

There will be no change of temperature in an adjoining uninvolved segment in the bowel which has been exposed in a similar manner. If at this time the involved segment is cut across, there is practically no bleeding and it is evident that there has been almost complete cessation of blood flow to the segment.

#### THE EXPERIMENTAL PROCEDURE

Fifteen mongrel dogs were divided into two groups, one of eight controls and one of seven animals which received  $\frac{1}{2}$  Gm. per kilogram

TABLE I

DOG	WEIGHT IN KG.	PREOPERATIVE SUCCINYLSULFATHIAZOLE	SURVIVAL TIME (HR.)
1	7.0	Control	12
2	8.0	Control	34
3	7.5	Control	30
4	10.0	Control	35
5	10.0	Control	45
6	10.0	Control	37
7	12.0	Control	37
8	12.5	Control	35
9	6.5	½ Gm./kg. for 10 days in the food	Until sacrificed one mo. P.O.
10	9.0	½ Gm./kg. for 10 days in the food	48
11	6.0	½ Gm./kg. for 10 days in the food	Until sacrificed one mo. P.O.
12	12.0	½ Gm./kg. for 10 days by stomach tube	24
13	11.0	½ Gm./kg. for 10 days by stomach tube	Until sacrificed 50 days P.O.
14	10.0	½ Gm./kg. for 10 days by stomach tube	Until sacrificed 50 days P.O.
15	10.5	½ Gm./kg. for 10 days by stomach tube	Until sacrificed 50 days P.O.

of body weight per day of succinylsulfathiazole for ten days before operation, as indicated in Table I. Bacteriologic studies on the stools of the treated animals showed a significant lowering of the coliform bacteria as reported by Poth, Knotts, Lee, and Inui.<sup>2</sup>

Under ether anesthesia and strict asepsis the veins of segments of ileum 50 cm. in length were ligated as indicated previously. The laparotomy wounds were then carefully closed. For the first forty-eight hours after operation water was given to the animals if they desired to drink, but food was withheld.

During the first twenty-four hours after operation all of the animals appeared extremely ill, and it was impossible to predict which individual dog would survive. The control group of animals ordinarily had bloody stools. This observation was less frequent in animals which had received succinylsulfathiazole therapy.

All of the control animals and two of those receiving preoperative succinylsulfathiazole therapy died during the first forty-eight-hour postoperative period. Immediate autopsy showed all of these animals to have a purulent peritonitis with blood in the peritoneal cavity and a bloody fluid in the intestinal loop. All of the control animals showed gross perforations of the involved segment. The two animals which had been treated with succinylsulfathiazole preoperatively did not show gross perforations of the ileum but at places only the serosa remained intact. The involved segments were purplish-black, gangrenous, and necrotic with large, jagged perforations measuring as much as 5 to 6 cm.

The animals which survived were sacrificed after thirty or fifty days. There were dense adhesions around the involved segment of ileum

which had acquired a striking collateral venous drainage. There veins were of three different sources; the most important ones were those in the omentum and in the previously avascular portion of the mesentery. The third less important venous collateral developed in the adhesions with loops of normal bowel. When these adhesions were separated, considerable bleeding occurred. Otherwise, this segment of bowel could not be distinguished from adjoining loops of ileum. Peristalsis was present and there was no evidence of dilatation or thickening of this portion of the bowel. The only observable change was in the microscopic appearance of the specimens taken after one month at which time there was some fibrosis in the muscularis. After fifty days, however, even these microscopic changes had disappeared and the segments were indistinguishable from normal ileum, except for the presence of adhesions and the atypical venous collaterals.

#### DISCUSSION

These two groups of experimental animals were subjected to identical operative procedures. One-half of the animals received succinylsulfathiazole for ten days during the preoperative period and again in the postoperative period beginning forty-eight hours after the operation, continuing for a period of two weeks. It is significant that within the first forty-eight hours after operation all the control animals had succumbed. When one considers the appearance of the segment of bowel, both immediately and at the time of the animal's death, it is inconceivable that merely altering the bacterial flora within the bowel would result in survival of the animal and eventual restoration of the involved segment to an essentially normal appearance and physiologic function. The fact that 70 per cent of the treated animals recovered is certainly significant and must indicate the profound effect the drug, succinylsulfathiazole, must have in altering the bacterial flora in the bowel. It cannot, of course, be concluded that the beneficial effects observed from the administration of succinylsulfathiazole are due entirely to the alteration of the bacterial flora. We do not, however, have any pertinent evidence at this time that the difference in behavior of the animals in the two groups is due to anything other than the alteration of the bacterial flora by this drug.

In view of the extensive damage to which these segments of bowel are subjected, it is likely that, if individuals exposed to blast injuries could receive succinylsulfathiazole prior to the trauma, the resulting late perforations would not occur.

These studies are being extended in an attempt to determine the mechanism by which injury occurs in the control animals as well as how this process is altered by the administration of succinylsulfathiazole and phthalylsulfathiazole.<sup>5-7</sup>

## SUMMARY

The ligation of the venous return from segments of ileum 50 cm. in length is always lethal. When the experimental animals have received therapeutic doses of succinylsulfathiazole, 70 per cent of the treated animals live indefinitely. The immediate and late changes occurring in segments of ileum in treated and untreated animals are described.

## REFERENCES

1. Poth, E. J., and Knotts, F. L.: Succinylsulfathiazole, a New Bacteriostatic Agent Locally Active in the Gastrointestinal Tract, *Proc. Soc. Exper. Biol. & Med.* 48: 129, 1941.
2. Poth, E. J., Knotts, F. L., Lee, J. T., and Inui, F.: Bacteriostatic Properties of Sulfanilamide and Some of Its Derivatives. I. Succinylsulfathiazole, a New Chemotherapeutic Agent Locally Active in the Gastrointestinal Tract, *Arch. Surg.* 44: 187, 1942.
3. Poth, E. J., and Knotts, F. L.: Clinical Use of Succinylsulfathiazole, *Arch. Surg.* 44: 208, 1942.
4. Poth, E. J.: Succinylsulfathiazole: An Adjuvant in Surgery of the Large Bowel, *J. A. M. A.* 120: 265, 1942.
5. Poth, E. J., and Ross, C. A.: Phthalylsulfathiazole, a New Bacteriostatic Agent, *Fed. Proc.* 2: 89, 1943.
6. Poth, E. J., and Ross, C. A.: Bacteriostatic Properties of Sulfanilamide and Some of Its Derivatives: II. Phthalylsulfathiazole, a New Chemotherapeutic Agent Locally Active in the Gastrointestinal Tract, *Texas Rep. Biol. & Med.* 1: 345, 1943.
7. Poth, E. J., and Ross, C. A.: The Clinical Use of Phthalylsulfathiazole, *J. Lab. & Clin. Med.* 29: 785, 1944.

# THE APPLICATION OF SUCCINYLSULFATHIAZOLE AND PHTHALYLSULFATHIAZOLE TO GRANULATION TISSUE: ABSORPTION AND EXCRETION\*

EDGAR J. POTH, M.D., PH.D., AND CHARLES A. ROSS, M.S.,  
GALVESTON, TEXAS

(From the Department of Surgery, the University of Texas Medical Branch)

THE interesting property of succinylsulfathiazole of poor absorability from the alimentary tract described by Poth, Knotts, Lee, and Inui in 1942<sup>1</sup> would naturally bring this compound under investigation in a search for a drug suited for topical application without general systemic effects. Although it has been shown that succinylsulfathiazole (Sulfasuxidine) is rapidly absorbed from peritoneal surfaces and from intramuscular and subcutaneous spaces, reports of slight absorption of sulfasuxidine from wounds and granulating surfaces have appeared.<sup>2, 3</sup> Pulvertaft and Mackenzie<sup>2</sup> make the claim from observed data that sulfasuxidine is split to yield sulfathiazole by the action of bacteria and plasma. Poth and Knotts<sup>4</sup> showed that sulfasuxidine is altered to yield a free sulfonamide when suspended in an emulsion of feces at 37° C.

In a recent editorial by Tennison<sup>3</sup> a degree of nonabsorbability of sulfasuxidine from granulating surfaces is claimed which does not conform with our observations. Tennison reports that when as much as 25 Gm. of sulfasuxidine is applied to raw surfaces caused by burns which involved as much as 45 per cent of the body surface there is no measurable absorption of the drug. In order to re-emphasize the limited absorption of sulfasuxidine from the gastrointestinal tract in contradistinction to the rapidity with which the drug is absorbed from subcutaneous and intramuscular spaces and from granulating surfaces this report is submitted.

## EXPERIMENTAL OBSERVATIONS ON THE RATE OF ABSORPTION OF SULFASUXIDINE† AND SULFATHALIDINE† FROM GRANULATING SURFACES

Weighed quantities of sulfasuxidine and sulfathalidine<sup>5, 6</sup> were powdered on measured areas of granulating surfaces and covered with either fine meshed, petrolatum gauze or a sheet of thin rubber tissue. Blood specimens were taken at 30-minute, 1-, 2-, 3-, 4-, 8-, 20-, 48- and 72-hour intervals and analyzed for both the free and conjugated forms

\*Supported by a grant from Sharp & Dohme, Philadelphia, Pa.

†Sulfasuxidine and Sulfathalidine are proprietary names for succinylsulfathiazole and phthalylsulfathiazole registered by Sharp & Dohme, Philadelphia, Pa.

Received for publication, April 13, 1944.

TABLE I

THE RATE OF ABSORPTION OF SUCCINYLSULFATHIAZOLE AND PHTHALYLSULFATHIAZOLE FROM GRANULATING SURFACES AND THEIR EXCRETION IN THE URINE\*

CONCENTRATION OF DRUG IN BLOOD MG. PER 100 C.C.			URINARY EXCRETION OF DRUG IN GM.	
HOUR	SULFATHIAZOLE	SUCCINYLSULFATHIAZOLE	SULFATHIAZOLE	SUCCINYLSULFATHIAZOLE
<i>10 Gm. Succinylsulfathiazole,† Petrolatum Gauze Bandage</i>				
4	0.0	2.9		
8	0.0	0.0		
12	0.0	0.0		
24	0.0	0.2	0.029†	4.126†
48	0.8	0.2	0.059†	0.232†
72	1.1	0.0	0.051†	0.049†
Total urinary excretion			0.138	4.407
Percentage of drug excreted			46.0%	
<i>10 Gm. Succinylsulfathiazole,† Rubber Bandage</i>				
½	1.3	1.9		
1	0.9	4.1		
2	0.3	5.9		
3	0.9	3.4		
4	0.0	2.8	0.015†	2.426†
8	0.3	1.5	0.028†	1.456†
24	0.0	0.7	0.016†	0.410†
48	-	-	0.000†	0.052†
Total urinary excretion			0.059	4.344
Percentage of drug excreted			44.3%	
<i>10 Gm. Phthalylsulfathiazole,§ Rubber Bandage</i>				
½	1.9	3.8		
1½	1.0	10.6		
2½	1.0	13.8		
3½	0.9	5.9		
4			0.009†	0.463†
7½	0.3	2.8		
8			0.087†	2.899†
24	0.1	0.0	0.044†	1.324†
48	0.0	0.2	0.042†	0.041†
Total urinary excretion			0.182	4.727
Percentage of drug excreted			49.9%	

\*Since the succinylsulfathiazole applied to the wound contained 4.22 per cent of sulfathiazole and the phthalylsulfathiazole contained 5.2 per cent of sulfathiazole, it is evident from the relative amounts of free and conjugated drug excreted in the urine that neither of these drugs is appreciably hydrolyzed in the area of the wound or during their passage through the patient. Area of granulations: 870 sq. cm.

†This sample of succinylsulfathiazole contained 4.22 per cent of free sulfathiazole.

‡Quantity of drug excreted in urine for the time interval indicated; that is, first 4 hours, 4 to 8 hours, 8 to 24 hours, etc.

§This sample of phthalylsulfathiazole contained 5.2 per cent of free sulfathiazole.

of the drug. Four-hour specimens of urine were collected for the same period and analyzed for the free and conjugated forms of the compounds. After 72 hours the dressings were removed and leached out with water. The ratio of free to conjugated drug in these washings was determined.

The following is a sample of a characteristic observation:

H. S., a 15-year-old male, had both legs burned eleven months previously. At present the granulating surfaces have a combined area of 870 sq. cm. and represent roughly 10 per cent of the total body surface. On successive weeks 10 Gm. of either sulfasuxidine or sulfathalidine were dusted onto the areas and covered



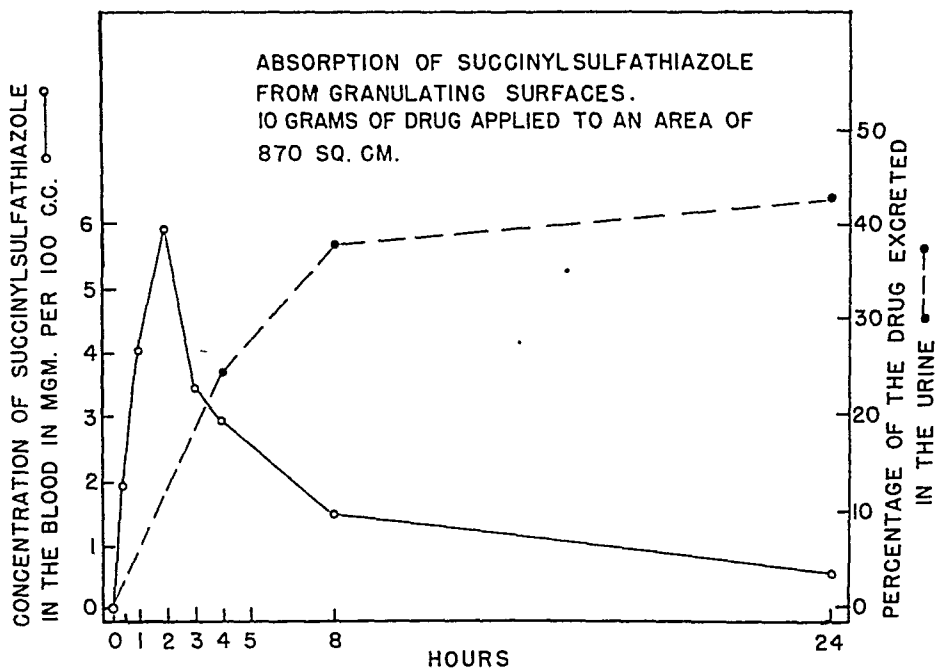


Fig. 1.—Absorption and excretion of succinylsulfathiazole applied to a granulating surface. The concentration of the drug in the blood is at its maximum in two hours and falls rapidly within eight hours. Thirty-eight per cent of the drug applied to the granulating surface is excreted in the urine within the first eight hours. After this period the concentration of total drug in the blood is insignificant. (See Table I.)

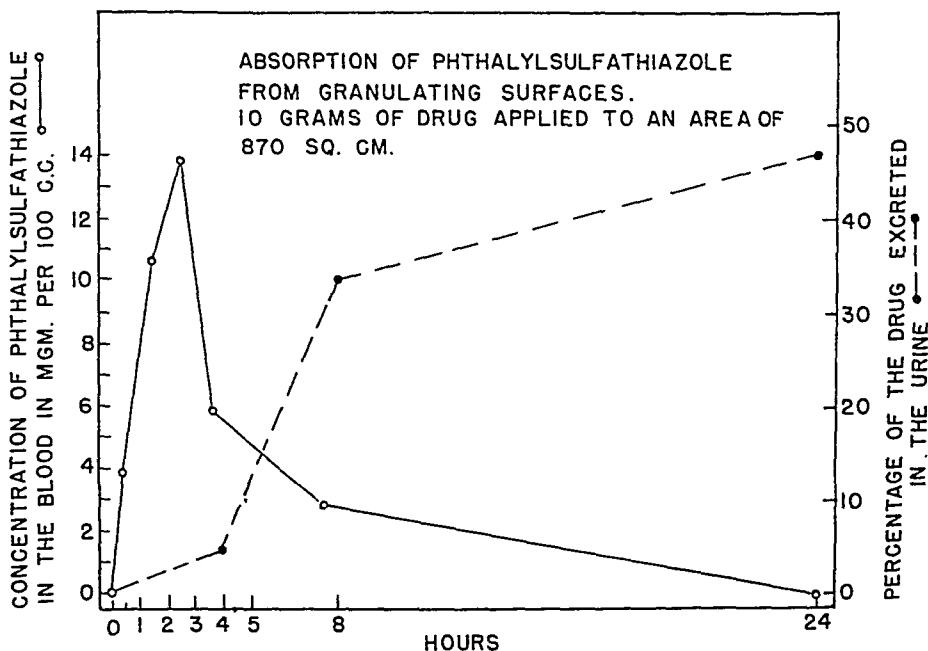


Fig. 2.—Absorption and excretion of phthalylsulfathiazole applied to a granulating surface. The concentration of the drug rises to a surprisingly high level within the first two and one-half hours and drops equally as rapidly thereafter. Thirty-five per cent of the drug applied to the granulating surface is excreted in the urine within the first eight hours. After this interval the concentration of total drug in the blood is insignificant. (See Table I.)

by thin rubber tissue or petrolatum gauze. Specimens were taken as previously described with the results as indicated in Table I and Figs. 1 and 2. Table II shows the observed blood concentrations and the excretion of the drug in the urine when 20 Gm. of succinylsulfathiazole were applied to the same surface daily and in this instance were covered by petrolatum gauze.

The bandages were removed after seventy-two hours and analyzed for residual drug. In the case of the succinylsulfathiazole the analysis showed 0.8 per cent of free drug, while for phthalylsulfathiazole 5.8 per cent of the drug was present as the free compound. These data indicate that the conjugated drugs have not been hydrolyzed on the dressings or while in contact with the granulating surfaces.

TABLE II

THE ABSORPTION OF SUCCINYLSULFATHIAZOLE FROM A GRANULATING SURFACE AND ITS EXCRETION IN THE URINE\*

CONCENTRATION OF DRUG IN BLOOD† MG. PER 100 C.C.			URINARY EXCRETION OF DRUG GM. PER 24 HR.	
DAY	SULFATHIAZOLE	SUCCINYLSULFATHIAZOLE	SULFATHIAZOLE	SUCCINYLSULFATHIAZOLE
1	0.9	0	0.046	2.194
2	0.9	0.2	0.077	7.478
3	1.3	0	0.178	3.791
4	0.9	3.8	0.079	5.696
5	0.5	0.2	0.079	4.225
6	1.4	0	0.099	1.713
7	1.3	0	0.083	3.133

\*The succinylsulfathiazole applied contained 4.22 per cent of free sulfathiazole. Area of granulations: 870 sq. cm. Daily application: 20 Gm. succinylsulfathiazole.

†Specimens taken 20 hr. after application of drug to the granulating surfaces.

# DISCUSSION

These studies demonstrate that succinylsulfathiazole and phthalylsulfathiazole are readily and rapidly absorbed from granulating surfaces although these compounds are but sparingly absorbed through the mucous membrane of the gastrointestinal tract. Roughly 50 per cent of the applied drugs are excreted in the urine within twenty-four hours with the major portion being absorbed from a granulating surface within the initial eight-hour period. After the first twenty-four hours, little drug appears in the urine, because the excess has either soaked into the dressing or has been otherwise carried from contact with the granulations. The low blood concentrations and the rapidity with which these drugs are excreted in the urine re-emphasizes our previous observations on the rapidity with which the compounds are excreted by the kidneys. Observations made on the concentration of the drugs in the blood alone do not indicate the degree and rapidity of absorption of these substances. In order to obtain a correct interpretation of absorption data, it is necessary to supplant such studies by determining the quantities of the free and conjugated forms of a drug excreted in the urine.

There is little reason to expect these compounds to be of great value in the local treatment of infected granulating surfaces. It has been shown that these compounds have but slight in vitro bacteriostatic activity. The ratio of the free and conjugated forms of the drugs excreted in the urine and found as a residue on the dressings indicates that little

of the compounds is split either by the bacteria present on the wounds studied or by the passage of the drugs through the body. Furthermore, since occasional toxic manifestations have been observed even when these compounds are administered orally with only slight absorption, it cannot be assumed with safety that these compounds can be used on granulating surfaces without considerable danger of occasional untoward systemic reactions.

An estimation of the value derived from the topical application of a substance to an infected granulating surface is difficult because of the many uncontrollable factors. We do not feel that any of the sulfonamide drugs can be recommended for topical use in treating infections such as occur on granulating surfaces, due to the fact that there are not sufficient data supporting their value, and the sulfonamides tend to increase scar and keloid formation. Furthermore, it is impossible to control the quantity of drug absorbed, and dangerously high blood levels occur rather frequently. Finally, the patient may become sensitized to the sulfonamide drugs and preclude their future use when the indications are more specific.

#### CONCLUSION

Both succinylsulfathiazole and phthalylsulfathiazole are rapidly absorbed when applied to granulation tissue. Urinary excretion studies indicate that these drugs are completely absorbed from granulating surfaces within twenty-four hours after application.

It cannot, therefore, be assumed that untoward reactions will not occur following the application of sulfasuxidine or sulfathalidine to granulating wounds, and their topical use is not recommended.

#### REFERENCES

1. Poth, E. J., Knotts, F. L., Lee, J. T., and Inui, F.: Bacteriostatic Properties of Sulfanilamide and Some of Its Derivatives: I. Succinylsulfathiazole, A New Chemotherapeutic Agent Locally Active in the Gastrointestinal Tract, *Arch. Surg.* 44: 187, 1942.
2. Pulvertaft, J. N., and Mackenzie, K. H.: Local Therapy of War Wounds: II. With Sulphasuxidine, *Lancet* 245: 379, 1943.
3. Tennison, C. W.: Use of Nonabsorbable Sulfasuxidine in Extensive Burns, *SURGERY* 15: 332, 1944.
4. Poth, E. J., and Knotts, F. L.: Clinical Use of Succinylsulfathiazole, *Arch. Surg.* 44: 208, 1942.
5. Poth, E. J., and Ross, C. A.: Phthalylsulfathiazole, A New Bacteriostatic Agent, *Fed. Proc.* 2: 89, 1943.
6. Poth, E. J., and Ross, C. A.: Bacteriostatic Properties of Sulfanilamide and Some of Its Derivatives: II. Phthalylsulfathiazole, A New Chemotherapeutic Agent Locally Active in the Gastrointestinal Tract, *Texas Rep. Biol. & Med.* 1: 345, 1943.

## A METHOD FOR THE LOCAL ADMINISTRATION OF PENICILLIN

COLONEL ELLIOTT C. CUTLER AND MAJOR WILLIAM R. SANDUSKY,  
MEDICAL CORPS, U. S. ARMY

*(From the Professional Services Division, Office of the Chief Surgeon,  
E.T.O., U. S. Army)*

THE purpose of this paper is to report a new method for the local administration of penicillin. The weight and volume of penicillin in relation to the effective dose is exceedingly small. This fact makes essential the use of some diluting substance, or vehicle, if uniform distribution to all parts of the local surface are to be attained.

The usual method of local application and the one used in the majority of instances in a group of casualties treated at U. S. Army station hospitals in the United Kingdom has been to dissolve the sodium salt of penicillin in sterile physiologic saline solution in amounts of 1,000 units per cubic centimeter. This solution is sprayed on the wound by means of an ordinary liquid atomizer. This has proved unsatisfactory because much of the solution runs off the surface and the amount retained in the wound is never accurately known. Many of the possible dry vehicles are undesirable because (1) they react unfavorably with penicillin, (2) they are not absorbable, and (3) they are chemotherapeutic agents themselves. Ointments are equally objectionable, particularly if primary closure of the wound is planned.

To overcome some of these objections we have used dehydrated human plasma as a vehicle for several months.

Under sterile conditions the sodium salt of penicillin is mixed with commercially prepared dehydrated plasma. From 10,000 to 20,000 units of penicillin to 0.2 Gm. of plasma is a desirable proportion; however, this ratio can be varied to fit the particular need. The plasma tends to be lumpy, but gentle stirring reduces it to a light fluffy powder. Penicillin is added, and after gentle stirring, a homogenous mixture is obtained. As plasma is used almost daily in our hospitals, we suggest, to avoid wastage, that the portion of plasma not mixed with the penicillin be used immediately for intravenous therapy.

Uniform distribution of this mixture on the wound surface is accomplished by means of a powder insufflator. A satisfactory inexpensive insufflator can be constructed from standard medical supply items (see Fig. 1).

When sprayed on a wound surface, the penicillin-plasma mixture immediately goes into solution and the tissues assume a yellow color. Complete hemostasis must be attained before insufflation; otherwise the mixture will be washed off at once. We have observed that 0.2 Gm. of plasma is sufficient for fine frosting of a surface 100 sq. cm. in area.

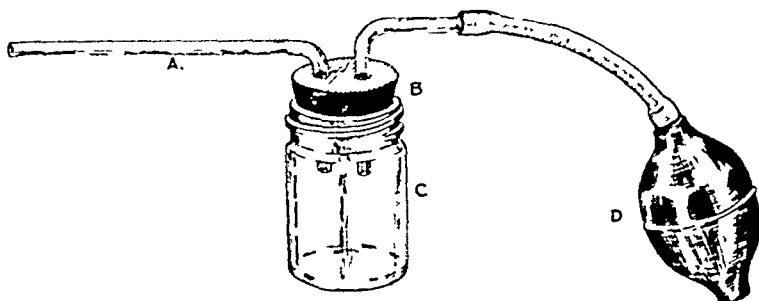


Fig. 1.—A powder insufflator constructed with materials obtained from U. S. Army medical supply items: *A* (44580), 6 mm. glass tubing; *B* (44200), two-hole rubber stopper; *C* (40830), sputum bottle; *D* (77025), rubber bulb hand atomizer.

Laboratory studies show no reduction in potency when penicillin is mixed with plasma. An admixture containing 5 units of penicillin and 0.05 Gm. of plasma was placed in a cylinder on an agar pour plate seeded with 1 c.c. of a twenty-four-hour culture of a test staphylococcus. After overnight incubation a zone of inhibition to bacterial growth 31 mm. in diameter was noted. Another mixture in the same proportion was prepared and refrigerated for ten days. The area of the zone of inhibition was essentially the same.

Experience with this method of local penicillin therapy at a station hospital has demonstrated its superiority over previous methods used. However, the preparation of the mixture as described here is time-consuming and is not practical for general use. Therefore, to obtain a product which can be readily and conveniently used it is suggested that penicillin be dissolved in liquid plasma and the resulting solution be dehydrated and distributed in appropriate sterile containers.

# PRIMARY CARCINOMA OF THIRD PORTION OF DUODENUM

THOMAS A. SHALLOW, M.D., SHERMAN A. EGER, M.D., AND  
JAMES B. CARTY, M.D., PHILADELPHIA, PA.

(From the Samuel D. Gross Surgical Division of the Jefferson Medical College Hospital)

**P**RIMARY carcinoma of the small intestine is a comparatively rare lesion and extremely so in the third portion of the duodenum. Since an opportunity seldom arises for radical resection of such a lesion, there being only twelve unquestionable cases reported, the following case is described in which a new operative procedure was successfully employed, its advantages discussed, and details of the other resected cases tabulated.

## CASE REPORT

*History.*—A 63-year-old white man was admitted to the Jefferson Medical College Hospital, July 27, 1943, on the medical service of Dr. Hobart A. Reimann. This patient had been in excellent health until one year prior to admission to the hospital, when epigastric fullness occurred about one-half to one hour after meals, and remained for several hours unless relieved by belching. No alkalies were taken. No particular type of food brought on an attack, which occurred every four to six weeks at the onset but gradually increased in frequency and severity. Between attacks he was entirely symptom-free. For two weeks prior to admission epigastric distress and fullness were constant, and were relieved only by vomiting. The vomitus was bile stained and contained particles of food ingested several meals previously but never any blood. Stools diminished in amount but otherwise were normal. There was twenty pounds loss in weight during the last six months, and most of this in the last two weeks. His past medical and family history were negative for ulcer or malignancy.

*Physical Examination.*—Abnormal findings consisted of mild dehydration, moderate epigastric distention, and a deep, firm, fixed, nontender mass two inches in diameter just above the umbilicus.

*Laboratory Data.*—The blood count showed hemoglobin 73 per cent, red cells 3,430,000, color index 1.07, and white cells 5,600 with a normal differential.

The gastric contents contained a residual total acidity of 25 and free hydrochloric acid of 20; after a test meal these figures gradually rose to a maximum of 48 and 27, respectively, in the sixth specimen. There was bile present in all the specimens, but blood and lactic acid were absent.

Urine examination was normal. The Wassermann and Kahn reactions of the blood serum were negative. The sedimentation rate was 24 mm. in one hour.

Roentgenographic study of the gastrointestinal tract (by Dr. Paul C. Swenson) showed almost complete obstruction at the beginning of the ascending loop of the duodenum. Flash roentgenograms (Figs. 1 and 2) did not demonstrate the outline of the tumor because the associated spasm and reverse peristalsis instantly returned the barium to the second portion. A re-examination following a period of gastric lavages revealed better tone to the stomach wall and less dilatation. There was again almost complete obstruction at the beginning of the ascending loop of the duodenum, behind which the barium puddled and the duodenum was dilated. Enough

Received for publication, June 3, 1944.



Fig. 1.—Roentgenogram following barium meal showing obstruction in the third portion of the duodenum



Fig. 2.—Roentgenogram twenty-four hours following barium meal demonstrating the gastric and duodenal retention.

barium could not be forced through the constriction at any time to allow for good contours. The diagnosis made was a lesion in the third portion of the duodenum, probably due to a malignancy, either primary or secondary.

*Operation.*—After the patient was transferred to the surgical service operation was performed Aug. 4, 1913. The abdomen was opened through an upper right

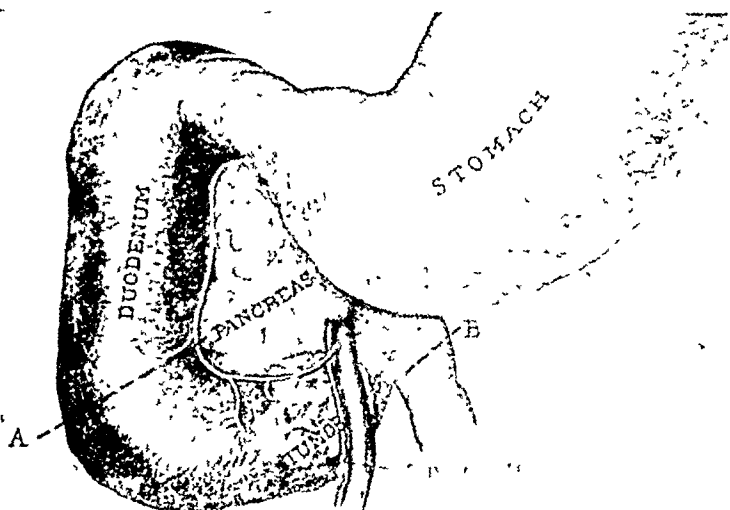


Fig. 3.—Anatomic relationship of tumor represented diagrammatically. Lines *A* and *B* are sites of resection

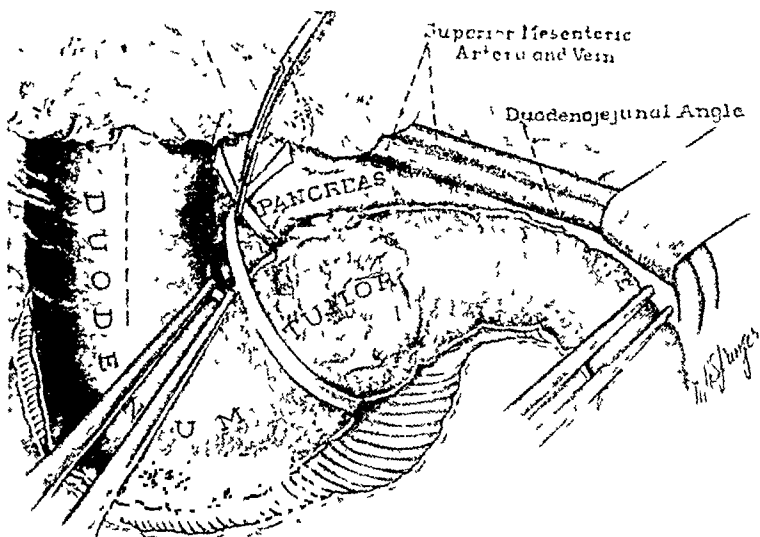


Fig. 4.—Third portion of duodenum and duodenojejunal angle mobilized prior to resection. Dotted line on second portion of duodenum represents site for side-to-side duodenojejunostomy.

rectus incision under spinal anesthesia. A tumor was found involving the postero-superior wall of the third portion of the duodenum beneath the superior mesenteric vessels (Fig. 3). The adjacent retroperitoneal tissue was indurated, but there was no evidence of extension of the growth or metastasis. The entire third portion of the duodenum was mobilized and resected (Fig. 4). The free ends of the bowel



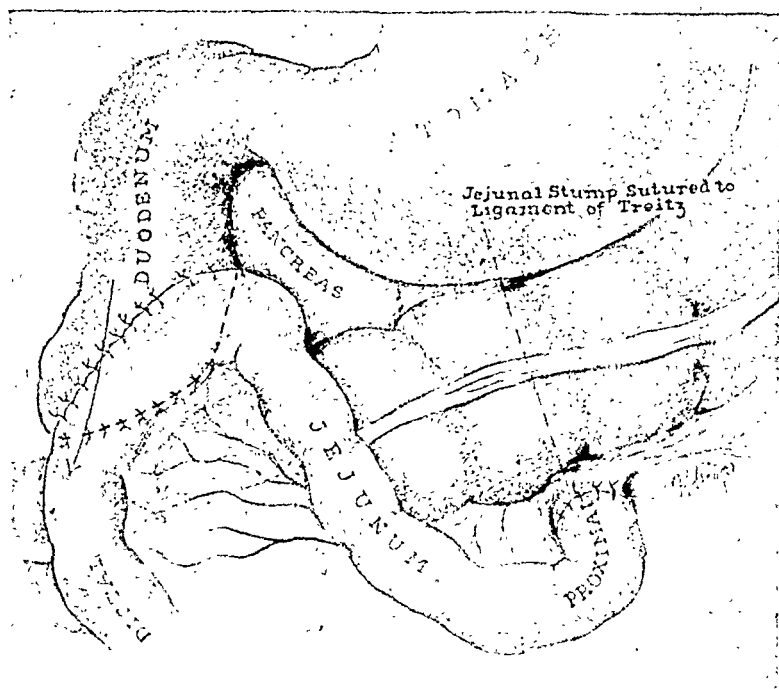
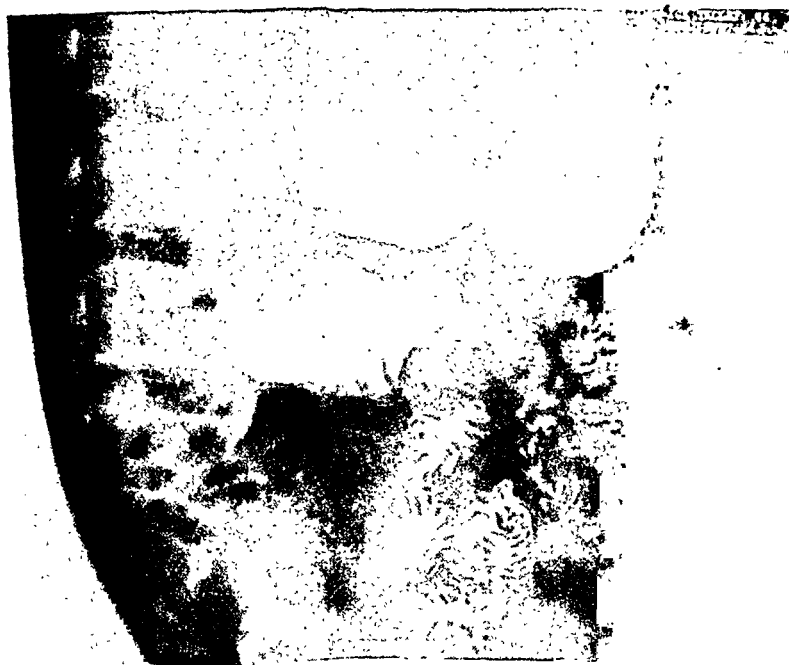


Fig. 5.—Side-to-side antecolic duodenojejunostomy completed. Proximal jejunal stump anchored to ligament of Treitz.



Following barium meal, 8 months postoperatively, revealing stomach and duodenojejunostomy functioning well.

were closed. An antecolic duodenojejunostomy (Fig. 5) was performed in a side-to-side manner anastomosing the jejunum, about ten inches from the ligament of Treitz, to the second portion of the duodenum, just distal to the ampulla of Vater. The suture line of the closed duodenal stump was reinforced by anchoring it to the posterior surface of the jejunum just distal to the anastomosis. The jejunal stump was reattached to the ligament of Treitz leaving the proximal jejunum available for a gastroenterostomy should the duodenojejunostomy stoma have proved inadequate. The abdomen was closed without drainage. The operating time was one hour and fifty minutes. The patient was discharged from the hospital Sept. 18, 1943.

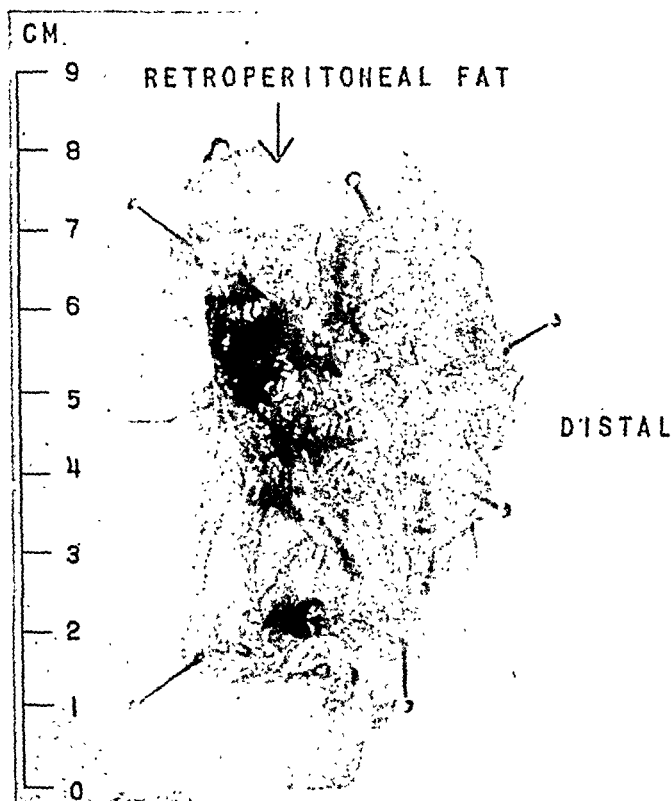


Fig. 7.—Opened specimen of ulcerative adenocarcinoma of third portion of the duodenum.

*Pathologic Report.*—The removed segment of duodenum contained a central penetrating ulcer 2 cm. in diameter (Fig. 7). In sections through the ulcer base, the epithelium was irregular and nonsecreting, arranged in small cords and acini (Fig. 8). The cells showed marked hyperchromatism and a few mitotic figures. They infiltrated the entire submucosa, submucosa, and a portion of the muscle layers. The supporting connective tissue was very scant, containing some plasma cells and lymphocytes. The diagnosis was primary ulcerative adenocarcinoma of the duodenum.

*Follow-Up.*—At the present time (nine months after operation) the patient is symptom-free, has gained thirty pounds in weight, and x-ray examination following a barium meal reveals no abnormality (Fig. 6).

We have been able to collect from the world literature reports of only twelve unquestionable cases of primary carcinoma of the third por-

tion of the duodenum in which resection was done. The third or inferior portion consists of both the horizontal and ascending segments, terminating at the duodenojejunal flexure. The cases reported by Allen,<sup>1</sup> Mallory,<sup>11</sup> Markus,<sup>12</sup> and Muller<sup>13</sup> are omitted because the growth was either not primary in the third portion of the duodenum or questionable as to its location.



Fig. 8.—Photomicrograph of section through ulcer base of tumor ( $\times 37.5$ ).

In Table I are listed the twelve collected cases and our case. It will be noted that there are five end-to-end anastomoses, three side-to-side, two end-to-side, one side-to-end, and one complete duodenectomy. The jejunum was stated to have been brought through the transverse mesocolon posterior to the superior mesenteric vessels in two cases and anterior in one. Two complementary gastroenterostomies were performed, one preliminary to a complete duodenectomy and the other in addition to an end-to-side duodenojejunostomy. The operative mortality was 17 per cent.

In our case a different operation was employed in which an antecolic side-to-side duodenojejunostomy was performed leaving a proximal jejunal loop. This procedure (Fig. 5) has the following advantages:

1. The anastomosis is safer for it is performed where the duodenum has a peritoneal covering.

TABLE I  
RESECTED CASES OF PRIMARY CARCINOMA OF THIRD PORTION OF DUODENUM

AUTHOR	PATIENT'S AGE (YRS.)	SEX	LOCATION OF TUMOR TO SUPERIOR MESENTERIC VESSELS	SIZE OF TUMOR (CM.)	OPERATIVE PROCEDURE AND TYPE OF DUODENOJEJUNOSTOMY	RESULTS
Syme <sup>15</sup>	40	M	Posterior	3.2	End-to-end	Well 3 mo. later
Davis <sup>4</sup>	46	F	Distal	4	End-to-end	Died 7 days later
Harries and Harrison <sup>6</sup>	49	F	Distal	1.5	End-to-end	Died 3 mo. later
Bergendal <sup>12</sup>	60	F	Distal	3.5	End-to-end	Well 20 mo. later
Graham <sup>7</sup>	54	F	Proximal	3	End-to-end (jejunum brought superior mesenteric vessels)	Died 3 mo. later
Lundberg <sup>10</sup>	64	M	Distal	1	End-to-side (jejunum brought superior mesenteric vessels)	Well 3 mo. later
Tatlow <sup>18</sup>	53	M	Distal	3	End-to-side (also used proximal jejunum for posterior vertical gastrojejunostomy)	Well 4 mo. later
Egers	50	F	Proximal	2.5	Side-to-side (retrocolic)	Died 6 yr. later
Handfield-Jones <sup>8</sup>	54	F	Posterior	1.5	Side-to-side (jejunum brought superior mesenteric vessels)	Well 16 mo. later
Panchet and Luquet <sup>14</sup>	61	F	Distal	1	Side-to-end	Well 1 yr. later
Clairborn and Dobbs <sup>3</sup>	47	M	Distal, first operation; also proximal, second operation	5	First stage, gastrojejunostomy; second stage (1 mo. later), complete duodenal resection and cholecystogastrostomy	Died 18 hr. later
Farinas Mayo <sup>6</sup>	50	F	Distal	4	Not stated	Not stated
Shallow, Eger and Carty	63	M	Posterior	2	Side-to-side (antecolic, 10 in. from ligament of Treitz)	Well 9 mo. later
Extremes, 40-64				Ave. size 3	End-to-end 5 Complete duodenectomy 1	Operative mortality 17%
Average, 56					End-to-side 2 Complimentary gastro- 2	
					Side-to-side 3 enterostomy 1	

2. The closed duodenal stump is reinforced by being buried in the undersurface of the distal jejunal loop.

3. With the anastomosis side-to-side the angles can be well fortified and the size of the stoma regulated without encroaching on the common bile duct, ampulla of Vater, or the blood supply of the remaining duodenum.

4. With the jejunum antecolic, obstruction from pressure by the superior mesenteric vessels and from the passage through the transverse mesocolon is avoided.

5. A proximal jejunal loop is provided for a gastrojejunostomy should the duodenojejunostomy stoma be inadequate.

#### SUMMARY AND CONCLUSIONS

A new operation is described and illustrated for re-establishing bowel continuity following resection of the third portion of the duodenum for primary carcinoma and its advantages are enumerated. We believe this method to be safer, simpler, and less time-consuming than those previously reported.

#### REFERENCES

1. Allen, C. I.: Primary Carcinoma of the Duodenum With Report of 11 Cases, *Am. J. Surg.* 40: 89-101, 1938.
2. Bergendal, A.: A Contribution to the Knowledge of Primary Duodenal Cancer, *Acta Radiol.* 20: 417-426, 1939.
3. Claiborn, L. N., and Dobbs, W. G. H.: Carcinoma of the Third Segment of Duodenum; Report of Case, *SURGERY* 4: 97-102, 1938.
4. Davis, C. R.: Carcinoma of Duodenum; Case Report; *Am. J. Cancer* 23: 337-338, 1935.
5. Eger, S. A.: Primary Malignant Disease of the Duodenum, *Arch. Surg.* 27: 1087-1108, 1933.
6. Farinas Mayo, L.: Carcinoma del Ángulo Duodeno-yejunal, *Bol. Liga contra el cáncer* 9: 210-214, 1934.
7. Graham, R. R.: Personal Communication; and Carcinoma of the Duodenum: in *Operative Surgery*, Ed. by Bancroft, F. W., New York, 1941, D. Appleton-Century Co., Inc., pp. 641-643.
8. Handfield-Jones, R. M.: Intrinsic Carcinoma of the Duodenum With Report of Successful Removal, *Lancet* 2: 1168-1170, 1938.
9. Harries, D. J., and Harrison, C. V.: Primary Carcinoma of the Small intestine, *Brit. M. J.* 1: 923-924, 1935.
10. Lundberg, S.: Cancer of the Duodeno-jejunal Flexure, *Acta chir. Scandinav.* 56: 417-424, 1924.
11. Mallory, T. B.: Case Records of the Mass. General Hospital, Case 24162, *The New England J. Med.* 218: 687-689, 1938.
12. Markus, H.: Magen-duodenaladenomatose mit Maligner Degeneration des Duodenaladenoms, *Klin. Wchnschr.* 12: 617-618, 1933.
13. Muller, J., quoted by Marchand, L., and Guibert, H. L.: Contribution à l'étude de la Lymphogranulomatose Duodénale. Les Possibilités Anatomiques d'Exérèse de la 3e Portion du Duodénum; *Ann. d'anat. path.* 16: 311-325, 1939.
14. Pauchet, V., and Luquet: Cancer de la Quatrième Portion du Duodénum, *Bull. Acad. de méd., Paris* 97: 276-279, 1927.
15. Syme, G. A.: Carcinoma of the Duodenum; Resection, Recovery, *Lancet* 1: 148, 1904.
16. Tatlow, E. T.: Three Consecutive Cases of Carcinoma of the Jejunum, *Lancet* 1: 991, 1912.

# SPONTANEOUS VENTRAL HERNIA

## REPORT OF A CASE

EDWARD WOLIVER, M.D., AND CHARLES M. SCOTT, M.D.

CINCINNATI, OHIO

(From the Department of Surgery, College of Medicine, University of Cincinnati, and the Cincinnati General Hospital)

VENTRAL hernias are protrusions of the abdominal viscera through the anterolateral abdominal wall occurring at points other than the inguinal, femoral, and umbilical openings. They may be of traumatic (including postoperative) or spontaneous origin. Those of spontaneous origin are less common and may arise in the linea alba, lumbar region, and semilunar line (Spiegel's hernia). Recently Zimmerman and co-workers<sup>1</sup> have suggested another type of spontaneous ventral hernia, produced by a "banding" of the fibers of the internal oblique and transversalis muscles. This paper is concerned with the latter type of hernia and a case recently encountered is reported.

### CASE REPORT

H. G. (No. 193246), a 54-year-old white, married, nulliparous female, was admitted to the Cincinnati General Hospital April 30, 1944, with a history of intermittent left lower abdominal pain for several years, with increasing constipation for over a year. On April 23, she had an attack of left lower abdominal pain relieved by catharsis. On April 27, the pain recurred but was not relieved by a cathartic. She began to have severe cramping pains on the left side which spread over the entire abdomen. In addition, she noted the presence of a mass in the left lower abdomen which had appeared, likewise, during previous attacks of pain. There was no history of loss of weight, abnormal stools, or digestive difficulties. The remainder of the history was negative except for a persistent skin rash over the right arm. On admission the temperature was 100.4° F.; pulse, 88; respirations, 20; and blood pressure, 170/100. The white blood count was 14,500; hemoglobin, 14.5 Gm. per cent; and urine, negative. Examination revealed an obese, acutely ill, white female lying flat in bed but becoming very restless during paroxysms of pain. Positive findings were limited to the abdomen which was very obese, distended, and diffusely tender. There was an ill-defined tender mass in the left lower quadrant measuring about 10 cm. in diameter. Peristalsis was audible, synchronous with pain; however, the abdomen was quiet between paroxysms. No impulse on coughing could be felt over the inguinal and femoral rings.

The patient was given nothing by mouth and received an enema which was not productive of feces or flatus. Parenteral fluids were administered. X-rays of the abdomen were interpreted as exhibiting paralytic ileus. The proctoscopic examination and barium enema were negative. Morphine, gr.  $\frac{1}{4}$ , was given prior to these examinations, and on the patient's return to the ward from the x-ray department her abdomen was much more relaxed. On further examination it became apparent that the mass was within the abdominal wall. It was believed that the patient had an incarcerated hernia which was interparietal. The patient had been under continuous observation for twelve hours, and it was only through this continued observation that the diagnosis of hernia was established. At operation an interparietal hernia was found lying between the external and internal oblique muscles and containing incarcerated omentum. The neck of the sac was

located just above and lateral to the internal inguinal ring in a defect of the internal oblique and transversalis muscles. The adhesions between the omentum and sac were freed. The omentum was reduced, the sac was ligated as high as possible, and the excess portion excised. The wound was closed in layers with silk, imbricating the external oblique aponeurosis in two layers. The postoperative course was uneventful and the patient was discharged on the seventeenth postoperative day.

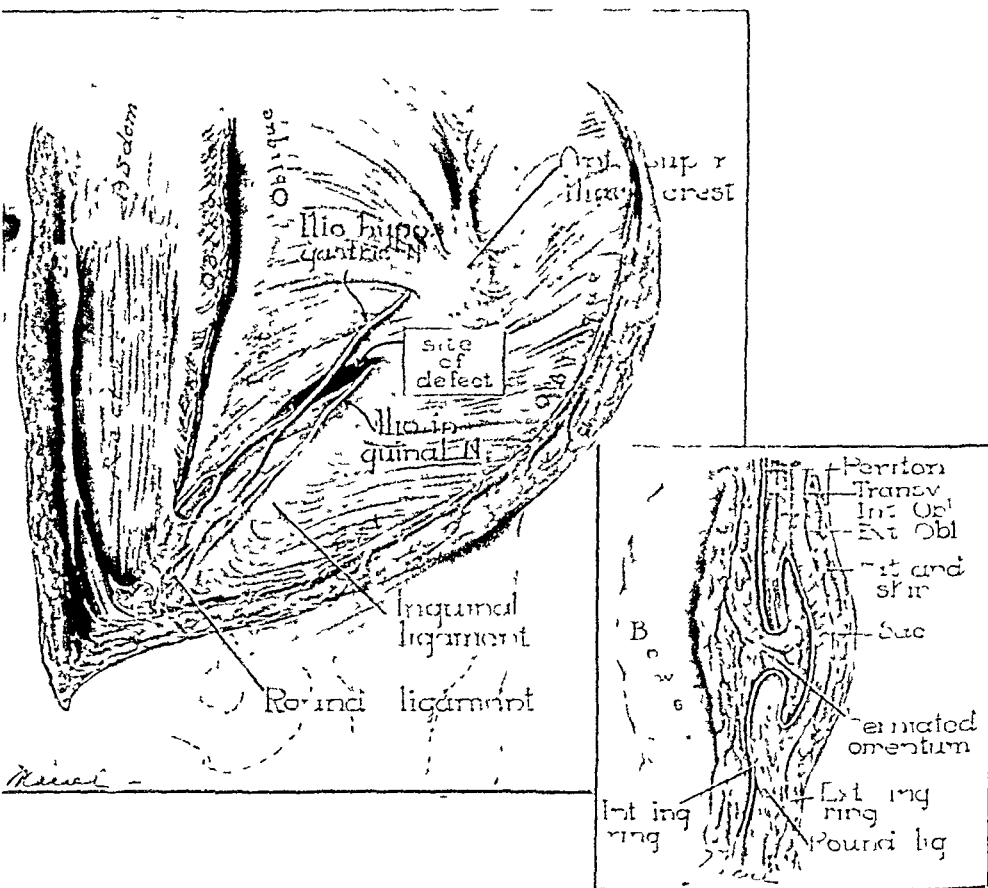


Fig. 1.—Diagrammatic sketch illustrating site of defect and position of hernia sac.

#### DISCUSSION

A confusion of classification has been found to exist among the group of ventral hernias. Interstitial hernias arising from defects above and lateral to the internal inguinal ring (as in the reported case) have been included previously in the group of interparietal inguinal hernias. Lower and Hicken,<sup>2</sup> in 1931, discussed the interparietal hernias of the inguinal region and presented two case reports. In each instance the sac did not communicate with the internal ring but arose from a defect above and lateral to the internal ring. Kronlein,<sup>3</sup> in 1876, referred to such a case as a "parainguinal interstitial hernia." It is our impression that such hernias differ from the group of true interparietal hernias and are more correctly classified as spontaneous ventral hernias.

Other differences exist between the two types. The sac of the true interparietal hernia is frequently multilocular, whereas in the spontaneous lateral ventral hernia the sac is usually unilocular. The former type of hernia is more frequent in the male, often being associated with an undescended testicle. This is not true of the latter type of hernia. Both types of hernias are similar in that the sac is located between the parietes, the contents frequently being incarcerated and strangulated. The diagnosis is, as a rule, difficult, and may be deferred until determined at the operating or autopsy room. Clinically the patient may complain of abdominal pain associated with an abdominal mass. In an obese patient it may be difficult to determine whether the mass is intraperitoneal or within the abdominal wall. There may be findings suggestive of intestinal obstruction requiring diagnostic sigmoidoscopic and barium enema studies. Incarcerated and strangulated omentum or bowel frequently are found in the sac. Other hernias may also be present. Zimmerman and associates<sup>1</sup> have recently presented a new concept concerning the pathogenesis of this type of hernia, reporting three such cases encountered at operation. They stressed the importance of the occurrence of defects due to banding of the transversalis and internal oblique muscles. These authors studied 500 body halves and discovered deficiencies which could permit of parietal herniation in 109 (21.8 per cent). These deficiencies consisted of slitlike gaps between divergent bundles of fiber. In some instances actual preperitoneal fat herniations were present. An additional congenital anatomic predisposition to hernia was suggested to us in our case. Fig. 1 illustrates how the ilioinguinal nerve emerged through the internal oblique muscle at the lateral angle of the defect. Examination of several cadavers revealed that this nerve, the iliohypogastric nerve, and the deep circumflex iliac artery perforate the internal oblique muscle at the site where such hernias usually occur and may predispose to the weakness.

The treatment, once the diagnosis has been established, is surgical. The interparietal position of the mass may confuse the operator until the external oblique aponeurosis is opened. The contents of the sac should be reduced or resected as is indicated and the sac ligated as high as possible. The parietal defect may be closed with sutures and the repair reinforced by imbricating the external oblique aponeurosis over the site of the defect.

#### SUMMARY

A case of spontaneous ventral hernia is reported. The etiological and clinical characteristics of this type of hernia are discussed.

#### REFERENCES

1. Zimmerman, L. M., Anson, B. J., Morgan, E. H., and McVay, C. B.: *Surg., Gynec. & Obst.* 78: 535-540, 1944.
2. Lower, W. E., and Hicken, N. F.: *Ann. Surg.* 94: 1070-1087, 1931.
3. Kronlein, R. V.: *Arch. f. Klin. Chir.* 19: 408-420, 1876.



# CONGENITAL EVENTRATION AT THE UMBILICUS

ALFRED H. IASON, M.D.,\* BROOKLYN, N. Y.

## DEFINITION

THE condition which is usually denominated a "congenital umbilical hernia," is an eventration contiguous to, or in, the umbilicus. About 300 years ago F. Rysch (*Observationum anatomico-chirurgicarum*, 1691) was the first to point out that "no hernia can be called umbilical before the umbilicus exists." The hernial contents were never in the abdominal cavity; they remained outside from the beginning of embryonal life and, consequently, prevented the formation of an umbilicus.

## SYNONYMS

The protrusive malformation at the umbilicus has been variously named congenital umbilical hernia, exomphalocele, omphalocele congenitalis, hernia funiculi umbilicalis, ectopia viscerum, amniotic hernia, or amniotic umbilicus.

## INCIDENCE

The congenital condition has an equal incidence in the sexes. It occurs in about one birth in 10,000.

A complete exomphalos is one in which the physiologic hernia into the celomic root of the umbilical cord, owing to the failure of closure of the ventral abdominal wall, persists until birth or shortly thereafter. (When only the abdominal wall is involved, the condition is termed gastroschisis completa.)

## PATHOLOGIC ANATOMY

The dilated root of the cord serves as the hernial sac (there is no true sac) which appears as a translucent membrane; the "neck" of this sac is encompassed by true skin definitely outlined, and the "fundus" is covered by the irregular network of blood vessels which combine to form the umbilical cord. (Cruveilhier first pointed out that a congenital umbilical hernia is characterized by the absence of a peritoneal sac.)

A disproportion in size between the viscera and the abdominal cavity may result in the condition where a viscus or viscera may remain extra-abdominal and at the base of the umbilical cord. The deciding factor is usually a failure of proper development of the abdominal wall. (See Fig. 1.)

\*Attending Surgeon, Adelphi Hospital; Director of Surgery, Brooklyn Home for the Aged.

Received for publication, April 12, 1944.

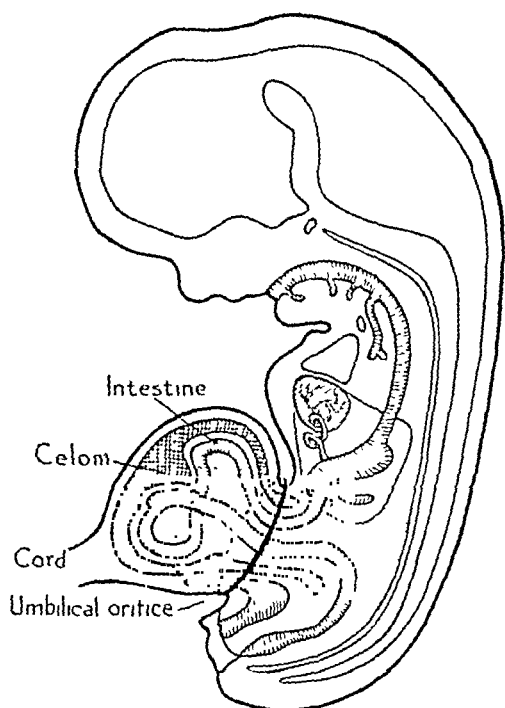


Fig. 1.—Seventeen millimeter human embryo, illustrating the position of the celomic cavity in the wide base of the umbilical cord.

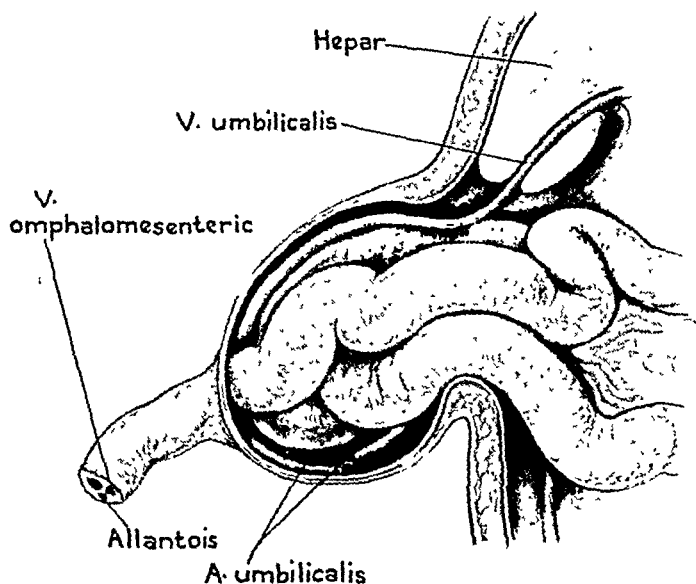


Fig. 2.—Congenital umbilical (cord) hernia, demonstrating contents and vessels.

A congenital defect remains at the umbilicus, either when the mid-gut fails to return to the abdominal cavity in the tenth week of intra-uterine life, or when, though it has returned, the extracelomic pouch of peritoneum fails to close. The failure may be of any degree. (See Fig. 2.)

In some cases the protrusion is ruptured during delivery and the infant is born eviscerated. When this does not occur, the abdominal wall appears to be replaced by a grayish translucent dome and the viscera can be seen through it, the cord being attached to the summit.

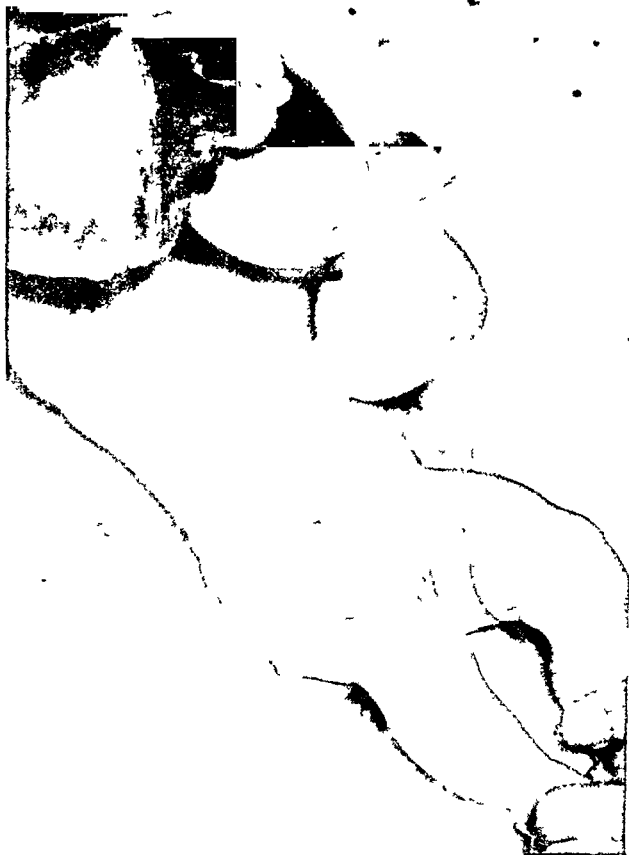


Fig 3 —Child 1 hr. old with congenital hernia into cord.

The displaced abdominal wall is to be found in the flanks contiguous to the protrusion. The junction between the abdomen proper and the exomphalic mass is distinctive in that there is an abrupt transition from pink skin to Wharton's jelly. The coverings of the mass are amnion, Wharton's jelly, and extracelomic peritoneum. (See Fig. 3.)

The sac is usually about 7 cm. in diameter, but may be as small as 2 cm., and the defect in the fascia varies from 5 to 8 cm. in diameter. The contents are small intestine and proximal colon with the addition,

in many instances, of the greater part of the liver and stomach and pelvic colon. Associated anomalies may be present, such as harelip, undescended testes, and clubfeet.

#### SYMPTOMS

A newborn infant with a complete exomphalos survives only a few hours. What is immediately obvious is the fact that the navel or umbilical cord is absent and in place thereof is a wide, central, funnel-shaped defect which is covered by translucent tissue of grayish hue, through which the viscera and accompanying structures are seen to project into the dilated root of the umbilical cord.



Fig. 4.—Closure of sac after reduction of contents (local anesthesia).

Although translucent and moist at birth, dehydration soon ensues and the sac becomes dry and friable, frequently tearing on manipulation. Should evisceration then occur, shock and death will be the inevitable result.

Eventration of less degree takes a variable form. The defect may consist in the mere thickening of the umbilical cord or in an obvious protrusion of intestinal content.

## DIAGNOSIS

There is a protrusive mass in the umbilical cord, with a grayish, translucent veil, beneath which the adumbrated viscera are enclosed.

## TREATMENT

In complete exomphalos treatment is obviously of no avail.

A small herniation into the umbilical cord is frequently curable in the newborn infant by means of a retaining apparatus, that is, adhesive plaster strapping containing an enclosed small button or a coin.

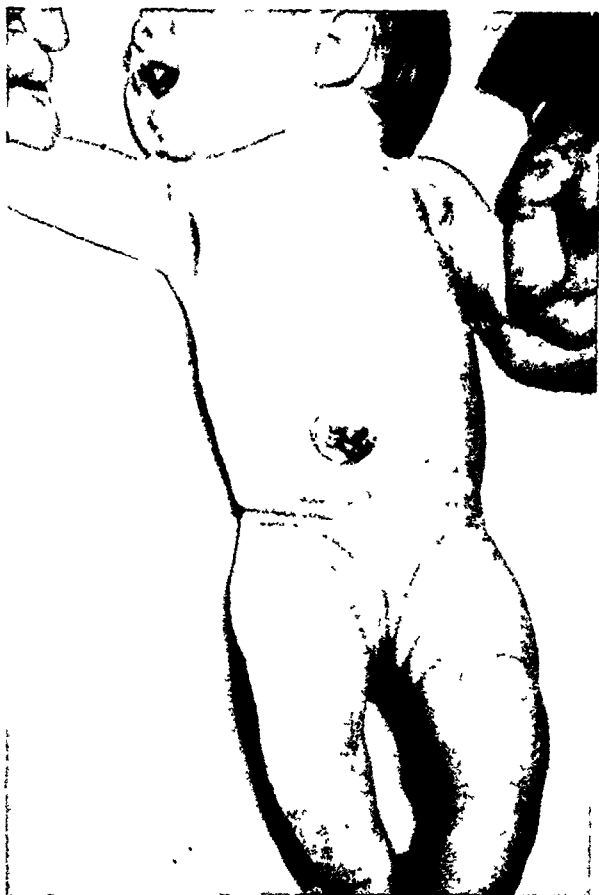


Fig. 5—Ten days after operation

## SURGICAL

The surgical treatment of this emergency is customarily carried out, when not contraindicated, soon after birth—within the first twelve hours. It has been widely observed that a newborn infant usually bears surgical procedures remarkably well if they are not too extensive or prolonged.

Local anesthesia only should be used.

TABLE I  
CONTENTS OF OMPHALOCELE

CASE	AGE (HR.)	SEX	DIAM- ETER OF OM- PHAL- OCELE (CM.)	INTES- TINE	COLON	LIVER	OTHER VIS- CERA	TREATMENT	RESULT
1	1	F	10	Plus	Plus	0	0	Surgery	Died
2	2	F	10	Plus	0	0	0	Surgery	Cured
3	4	M	7	Plus	Plus	0	0	Surgery	Cured
4	4	F	7	Plus	Plus	0	0	Surgery	Cured

The skin margin should be dissected from the subjacent rectus sheath and transversalis fascia, being careful not to tear or cut the sac wall, for there is danger of injuring a protruding viscus or permitting extrusion of the sac contents. The viscera are placed within the abdominal cavity before opening the sac to eliminate unnecessary trauma, to prevent evisceration and shock, and to obviate the possibility of infection. (See Fig. 4.)

After reduction, the two umbilical arteries and the umbilical vein are ligated.

One or two fingers are inserted into the opening by pressure from without the sac wall to maintain the viscera within the abdominal cavity. A continuous chromic suture, No. 1 or No. 2, on a Mayo needle is then inserted circumferentially to include the posterior rectus sheath and the transversalis fascia. This is then tied carefully so as not to impinge upon a loop of bowel or omentum. The anterior rectus sheaths are then approximated after excising the redundant part of the sac. In this manner it is not necessary to pass a suture through the neck of the sack which tears very easily.

If there is any doubt of the feasibility of approximating the rectus sheaths with a chromic suture, black silk may be used as a through-and-through stitch, including the skin and the abdominal aponeurosis. (See Fig. 5.)

#### COMPLICATIONS

Respiratory embarrassment may ensue because of displacement of the diaphragm as a result of increased intra-abdominal tension. Cases of paralytic ileus have been reported from pressure on the intestine.

## A SHARP DISSECTOR FOR MENISCECTOMY

CAPTAIN RAYMOND E. BUIRGE, MEDICAL CORPS, U. S. ARMY

THE removal of a semilunar cartilage is a common procedure, yet it may still be a rather difficult one in spite of the exposure provided by any incision<sup>1</sup> of choice. An additional posterior capsular incision<sup>2, 3</sup> is often useful in freeing the posterior attachment of the meniscus. Numerous instruments<sup>4-12</sup> have been designed to lessen the difficulties attending the operation of meniscectomy.

The use of an adequate single incision into the joint to accomplish the entire removal of the semilunar cartilage may be desired. Two instruments (Fig. 1) were devised to be used in excision of the medial semilunar cartilage through an anterior incision into the joint.

A modified Jones incision is used in the skin. The incision into the joint extends from a point, the leg hanging at a right angle, 0.5 cm. medial to the apical attachment of the ligamentum patellae obliquely downward and posterior, dividing the fibrous fanlike membrane of the tibial collateral ligament<sup>13</sup> and ending at the parallel fibers on a level with the coronary ligament.

The cartilage is usually freed anteriorly with ease. The liberation of the central portion of the cartilage is begun by the delineation of the superior and inferior capsular reflections which are separately divided along the periphery of the cartilage by the broad sharp dissector. By means of traction tension on the cartilage, the areolar tissue binding the cartilage to the parallel portion of the tibial collateral ligament is made taut and easily separated with the dissector.

The oblique portion of the tibial collateral ligament is inseparably united to the joint capsule posteriorly and, accordingly, has been demonstrated<sup>14</sup> to be joined to the meniscus. The knee is hyperflexed which allows the tibial collateral ligament to slide backward,<sup>15</sup> permitting easier access to the posterior capsular attachment of the cartilage. The limited exposure can be further improved by adduction or abduction and rotation of the tibia on the femur combined with digital pressure on the posterior joint capsule. The narrow dissector is employed to divide the superior and inferior capsular folds and the fibrous tissue uniting the capsule and the fibrocartilage. The freed cartilage is dislocated into the intercondylar notch, and its posterior limb between the lateral meniscus and the posterior cruciate ligament is divided under direct vision with the broad dissector.

These instruments were found to be a satisfactory addition to the usual devices used to remove the semilunar cartilage.<sup>15</sup> They are readily constructed<sup>6</sup> from sharp periosteal elevators.

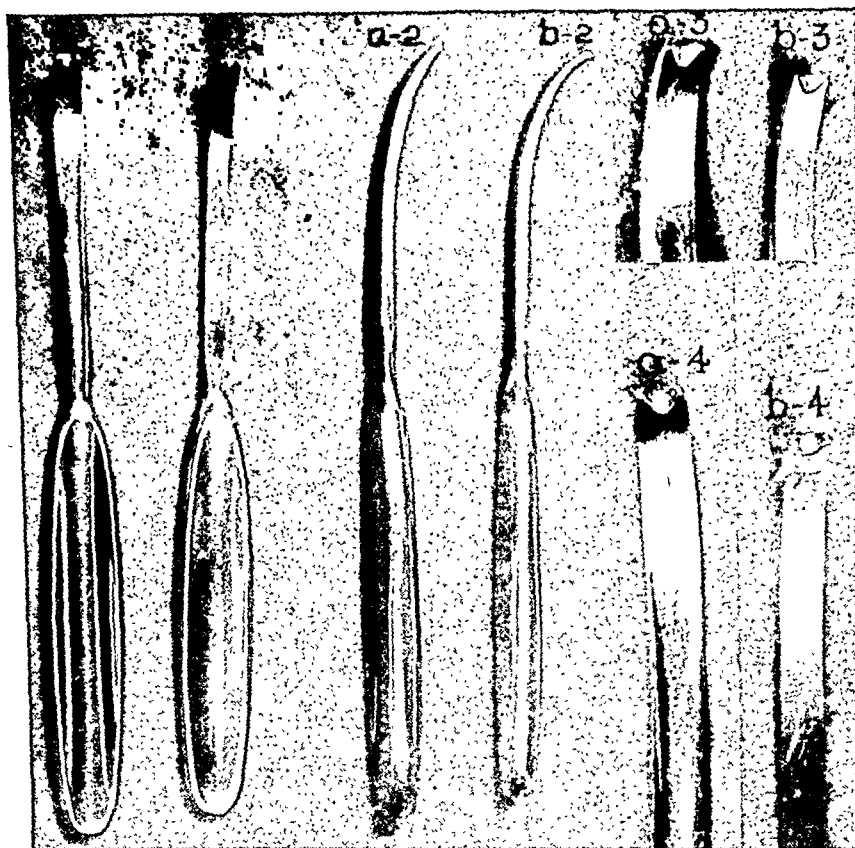


Fig. 1.—Photograph of cartilage dissectors. *a-1*,  $\frac{4}{5}$  actual size; broad dissector. *b-1*,  $\frac{4}{5}$  actual size; narrow dissector. *a-2*, side view, curved approximately 115 degrees. *b-2*, curved approximately 130 degrees. *a-3*, enlarged  $1\frac{2}{5}$  times. *b-3*, oblique view of concave cutting edge showing blunted outer margins. *a-4* and *b-4*, end view enlarged  $1\frac{2}{5}$  times.

#### REFERENCES

1. Jones, R., and Lovett, R. W.: Orthopedic Surgery, New York, 1923, William Wood & Co., p. 34.
2. Cave, E. F.: Combined Anterior-Posterior Approach to the Knee Joint, *J. Bone & Joint Surg.* 17: 427-430, 1935.
3. Bosworth, David M.: An Operation for Meniscectomy of the Knee, *J. Bone & Joint Surg.* 19: 1113-1116, 1937.
4. Steinmann, F.: Fracture Surgery, *Internat. Clin.* 4: 221-225, 1926.
5. Fairbank, H. A. T.: Meniscotomy Knife, *Lancet* 1: 24, 1929.
6. Leggiadro, Vincent: A New Electric Meniscotomy Knife, *J. Bone & Joint Surg.* 19: 246, 1937.
7. Lowe, Frank A., and Breck, Louis W.: A New Knife for Use in Removing Semilunar Cartilages, *J. Bone & Joint Surg.* 20: 220, 1938.
8. Haggart, G. E., and Toumey, James W.: Knee Joint Arthrotomy for Removal of a Semilunar Cartilage: Technic of the Lateral and Anterior Incisions, *S. Clin. North America* 19: 709-714, 1939.

\*Made by Pfc. William Nelson, Medical Detachment, Oliver General Hospital, Augusta, Ga.



9. Mercer, Walter: A New Knife for the Removal of the Meniscus, *J. Bone & Joint Surg.* 21: 744, 1939.
10. Dunlap, K.: Method for Complete Removal of the Semilunar Cartilage, *J. Bone & Joint Surg.* 24: 929-931, 1942.
11. Mitchell, Alexander: Meniscotomy Knife, *Lancet* 244: 528, 1943.
12. Freiberg, Albert H.: The Removal of the Meniscus From the Knee-Joint, *J. Orth. Surg.* 3: 697-698, 1921.
13. Brantigan, O. C., and Voshell, A. F.: The Tibial Collateral Ligament: Its Functions, Its Bursae, and Its Relation to the Medial Meniscus, *J. Bone & Joint Surg.* 25: 121-131, 1943.
14. Brantigan, O. C., and Voshell, A. F.: The Mechanics of the Ligaments and Menisci of the Knee Joint, *J. Bone & Joint Surg.* 23: 44-66, 1941.
15. Buirge, Raymond E.: Disabilities of the Knee (A Survey of 283 Admissions to the Oliver General Hospital). Unpublished data.

# Notices

---

## UROLOGY AWARD

The American Urological Association offers an annual award "not to exceed \$500" for an essay (or essays) on the result of some specific clinical or laboratory research in urology. The amount of the prize is based on the merits of the work presented, and if the Committee on Scientific Research deems none of the offerings worthy, no award will be made. Competitors shall be limited to residents in urology in recognized hospitals and to urologists who have been in such specific practice for not more than five years. All interested should write the Secretary, for full particulars.

The selected essay (or essays) will appear on the program of the forthcoming June meeting of the American Urological Association.

Essays must be in the hands of the secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis, Tenn., on or before March 15, 1945.

---

## AMERICAN COLLEGE OF SURGEONS EXPANDS GRADUATE TRAINING PROGRAM

In expanding its program of Graduate Training in Surgery to assure adequate opportunities for advanced training in surgery, particularly for recent medical graduates when they return from service with the Armed Forces, the American College of Surgeons has enlarged its headquarters staff in Chicago and announces the following new appointments effective immediately:

Major General Charles R. Reynolds (M.C., Retired), former Surgeon General of the U. S. Army, has been appointed Consultant in Graduate Training in Surgery. General Reynolds was in the Army from 1900 to 1939; served in the Philippine Insurrection; was Chief Surgeon of the Second Army, A.E.F., in World War I; was Commandant of the Army Field Service Medical School, Carlisle, Pa., from 1923 to 1931; and was Surgeon General of the Army from 1935 to 1939. He has been Director of the Tuberculosis Control Program of the Pennsylvania State Health Department for the past four years.

Dr. George H. Miller, formerly Dean of the Faculty of Medicine and Chairman and Professor of the Department, American University of Beirut, Lebanon, Syria, has been appointed Director of Educational Activities. Dr. Miller served in the U. S. Army Medical Corps, A.E.F., in 1918 and 1919; was Associate Professor of Pharmacology and later Associate Professor of Medicine of the State University of Iowa College of Medicine between 1922 and 1932; and was with the American University of Beirut from 1932 to 1944.

The Department of Graduate Training in Surgery is under the general direction of Dr. Malcolm T. MacEachern, Chairman of the Administrative Board, working with that board, and responsible to the Committee on Graduate Training in Surgery, of which Dr. Dallas E. Phemister of Chicago is chairman, and to the Board of Regents. In addition to General Reynolds and Dr. Miller, the staff of the department consists of Dr. Paul S. Ferguson, Director of Surveys, and three assistants who conduct the surveys, and the field representatives conducting the regular Hospital Standardization surveys under the direction of Dr. E. W. Williamson, Assistant Director of the College, who assist as required in the graduate training program. The latter is a development of the basic work of the college in stimulating the improvement of hospital service.

Surveys of hospitals for Graduate training in Surgery have been conducted since 1937 by the college. When the war ends in Europe, in order to satisfy the demands of men whose training in surgery was interrupted by war service, together with those of current medical graduates, sufficient opportunities should be ready in order to offer approved training to men who wish to become surgeons, Dr. MacEachern declares, adding that a competent surgeon according to present-day ideas requires a preparation of three or more years of systematic, supervised graduate training in general surgery or a surgical specialty, following a general internship and graduation from an acceptable medical school.

# Book Reviews

---

## Books Received

The receipt of books is acknowledged in this section and this treatment must be regarded as sufficient acknowledgement of the courtesy of the senders. Selections will be made for more extensive review dictated by the interests of our readers and as space permits.

**SURGICAL CLINICS OF NORTH AMERICA.** Lahey Clinic Number. Cloth. Pp. 740, with 275 illustrations. Philadelphia, 1944, W. B. Saunders Company.

**TEXTBOOK OF GYNECOLOGY.** By Emil Novak, M.D., F.A.C.S. Cloth. Price \$8. Pp. 708, with 456 illustrations. Baltimore, 1944, Williams & Wilkins Company.

**SURGICAL DISORDERS OF THE CHEST.** By J. K. Donaldson, Major Medical Corps. Cloth. Price \$6.50. Pp. 364, with 127 illustrations. Philadelphia, 1944, Lea & Febiger.

**HYPERTENSION AND HYPERTENSIVE DISEASE.** By Goldring and Chasis, New York University College of Medicine. Cloth. Price \$3.50. Pp. 253. New York, 1944, Commonwealth Fund.

**X-RAY EXAMINATION OF THE STOMACH.** By Fredric E. Templeton, Department of Roentgenology, The Cleveland Clinic. Cloth. Price \$10. Pp. 516. Chicago, 1944, University of Chicago Press.

**THE ART OF ANESTHESIA.** By Dr. Pamel J. Flagg, Visiting Anesthetist to Manhattan Eye and Ear Hospital. Cloth. Price \$6. Pp. 506. Philadelphia, 1944, J. B. Lippincott Company.

**A HANDBOOK OF ROENTGEN DIAGNOSIS OF THE GASTROINTESTINAL TRACT.** By Fred Jenner Hodges, B.S., M.D., Professor of Roentgenology, University of Michigan Medical School, Ann Arbor, Mich. Cloth. Price \$5.50. Pp. 320. Chicago, 1944, The Year Book Publishers, Inc.

**EMERGENCY SURGERY.** By Hamilton Bailey, F.R.C.S., Surgeon, Royal Northern Hospital, London. Cloth. Price \$18. Pp. 969, with 1039 illustrations. Baltimore, 1944, Williams & Wilkins Company.

**CATARACT AND ANOMALIES OF THE LENS.** By John G. Bellows, M.D., Ph.D., Assistant Professor of Ophthalmology, Northwestern University Medical School, Chicago. Cloth. Pp. 624, with 208 illustrations and 4 color plates, St. Louis, 1944, The C. V. Mosby Co.

**CLINICAL UROLOGY, Vol. 1 and Vol. 2.** By Oswald Swinney Lowsley, Director Department of Urology of the New York Hospital and Thomas Joseph Kirwin, Attending Surgeon of the Department of Urology of the New York Hospital. Cloth. Price \$10 per set. Pp. 942 (Vol. 1) and pp. 1769 (Vol. 2). Baltimore, 1944, Williams & Wilkins Company.

**METABOLISM MANUAL.** By Jessie Lex, ASCP, R.T., M.T., President Illinois Society Clinical Laboratory Technicians, Peoria, Ill. Cloth. Pp. 56. Baltimore, 1943, The Waverly Press.

**THE FLOW OF WATER THROUGH THE KIDNEY.** By Dr. Felix Fuchs. Cloth. Pp. 100. New York, 1944, Commonwealth Fund.

**GYNECOLOGY AND GYNECOLOGIC NURSING.** By Norman F. Miller, M.D., Professor of Obstetrics and Gynecology, University of Michigan Medical School. Cloth. Price \$2.75. Pp. 378, with 227 illustrations. Philadelphia, 1944, W. B. Saunders Company.

**OPERATIONS OF GENERAL SURGERY.** By Thomas G. Orr, M.D., Professor of Surgery, University of Kansas, School of Medicine, Kansas City, Kan. Cloth. Pp. 723, with 1396 illustrations and 570 figures. Philadelphia, 1944, W. B. Saunders Company.

**STRUCTURE AND FUNCTION AS SEEN IN THE FOOT.** By Frederic Wood Jones, D.Sc., Professor of Anatomy, University of Manchester. Cloth. Price \$7.50. Pp. 329. Baltimore, 1944, Williams & Wilkins Company.

**THE RADIOLOGY OF BONES AND JOINTS.** By James F. Brailsford, M.D., Ph.D., Hunterian Professor Royal College of Surgeons, England. Cloth. Price \$12. Pp. 440, with 404 illustrations. Baltimore, 1944, Williams & Wilkins Company.

**ORTHOPAEDIC SURGERY.** By Walter Mercer, M.B., Assistant Surgeon, Royal Infirmary, Edinburgh. Cloth. Price \$12. Pp. 947. Baltimore, 1943, Williams & Wilkins Company.

**DISEASES OF THE DIGESTIVE SYSTEM.** By Sidney A. Portis, Associate Professor of Medicine, University of Illinois Medical School. Cloth. Pp. 932, with 182 illustrations. Philadelphia, 1944, Lea & Febiger.

**PRINCIPLES AND PRACTICE OF SURGERY.** By W. Wayne Babcock, M.D., Philadelphia General Hospital, Philadelphia. Cloth. Pp. 1331, with 1141 illustrations and 8 colored illustrations. Philadelphia, 1944, Lea & Febiger.

# INDEX TO VOLUME 16

## AUTHORS INDEX\*

In this index following the author's name, the title of the subject is given as it appeared in the JOURNAL. Editorials are also included in the list and are indicated by (E).

### A

- ADAIR, FRANK E. Primary lymphosarcoma of breast, 836  
ADAMS, R. CHARLES, AND DIXON, CLAUDE F. Anesthesia in thyroid surgery, 700  
ASTWOOD, E. B. Chemotherapy in hyperthyroidism, 679

### B

- BARONOFKY, IVAN D. Urobilinogen test as additional aid in early recognition of fecal fistula, 377  
BARR, DAVID P. Medical management of thyrotoxicosis, 668  
BELLIS, CARROLL J. Cystometry after spinal anesthesia, 896  
BERGMAN, H. C. (See Prinzmetal, Bergman, and Hechter), 906  
BLACK, B. MARDEN. (See Pemberton and Black), 756  
BROCKBANK, MARK J. (See Floyd and Brockbank), 403  
BRODERS, ALBERT C., AND PARKHILL, EDITH M. Diffuse and adenomatous goiter and goiter induced by various agents, 633  
BRODY, BERNARD S. (See German, Brody, and Harvey), 874  
BRUNSCHWIG, ALEXANDER. Survival of rhesus monkey four years after excision of head of pancreas with occlusion of external pancreatic secretion, 416  
—, AND NICHOLS, SABRA. Retention of intravenously infused gelatin, 923  
BUIRGE, RAYMOND E. Experimental observations on human ileocecal valve, 356  
—, Sharp dissector for meniscectomy, 956  
BURGER, RAY E., AND LEHMAN, EDWIN P. Leontiasis ossea complicated by Marjolin's ulcer, 542  
BUXTON, ROBERT W. Problem of thyroid crisis, 748

### C

- CAHILL, GEORGE F. Hormonal tumors of adrenal, 233

- CARTY, JAMES B. (See Shallow, Eger, and Carty), 939  
CLUTE, HOWARD M., KENNEY, FRANCIS R., AND HAMILTON, BURTON E. Management of postoperative complications in thyroid surgery, 739  
COLE, WARREN H. Factors influencing operability and mortality rate in goiter, 688  
—, Progress and future in treatment of goiter, 811 (E)  
COOPER, WILLIAM GRANT, II, ZUMWALT, WILMA, AND SUGARBAKER, EVERETT D. Limited comparison of continuous spinal and general ether anesthesia, 886  
COPE, OLIVER. Endocrine aspect of enlargements of parathyroid glands, 273  
CREEVY, C. D. Meeting of American association of genitourinary surgeons, 466  
CUTLER, ELLIOTT C., AND SANDUSKY, WILLIAM R. Method for local administration of penicillin, 937

### D

- DAVIDOFF, LEO M. Endocrinologic aspects of tumors of pineal gland, 306  
DEAN, ARCHIE L., WOODARD, HELEN Q., AND TWOMBLY, GRAY H. Endocrine treatment of cancers of prostate gland, 169  
DIXON, CLAUDE F. (See Adams and Dixon), 700  
DOSS, A. KELLER. Translumbar aortography; apparatus for injecting radiopaque media, 422

### E

- EGER, SHERMAN A. (See Shallow, Eger, and Carty), 939

### F

- FARROW, JOSEPH H. Effect of sex hormones on skeletal metastases from breast cancer, 141  
FICARRA, BERNARD J., AND NACLERIO, EMIL A. Physiochemical disturbance in severe burn, 529

\*July, pp. 1-168; August, pp. 169-318; September, pp. 319-476; October, pp. 477-632; November, pp. 633-814; December, pp. 815-972.

- FINDLEY, THOMAS. Obligations of internist to general surgeon, 567 (E)
- FISHBACK, F. C. Twenty-fifth meeting of American association for thoracic surgery, 620
- FLOYD, JOE R., AND BROCKBANK, MARK J. Spool cotton as suture material, 403
- FREED, S. C., KRUGER, H. E., AND PRINZMETAL, MYRON. Role of bacteria in shock due to crushed muscle in dogs, 914

## G

- GARDNER, W. C. Tumors in experimental animals receiving steroid hormones, 8
- GERMAN, WILLIAM J. Endocrine effects of pituitary tumors, 47
- , BRODY, BERNARD S., AND HARVEY, SAMUEL C. Compound cranio-cerebral injuries, 874
- GORE, IRA, AND MCCARTHY, ALPHONSUS M. Boeck's sarcoid, 865
- GREENWALD, WILLIAM. Papilloma of gall bladder, 370
- GURDJIAN, E. S., AND WEBSTER, JOHN E. Acute physiologic responses in experimental head injury with special reference to mechanism of death soon after trauma, 381
- GUTHRIE, DONALD, AND SCHIMMEL, IRWIN. Drainage in thyroidectomy, 725

## H

- HAMILTON, BURTON E. (See Clute, Kenney, and Hamilton), 739
- HARVEY, SAMUEL C. (See German, Brody, and Harvey), 874
- HECHTER, OSCAR. (See Prinzmetal, Bergman, and Hechter), 906
- HEIMAN, HELEN I. (See Kaufman and Heiman), 557
- HERRMANN, JULIAN B. (See Adair and Herrmann), 836
- HOLINGER, PAUL H. Twenty-sixth annual meeting of American broncho-esophagological association, 470
- HORN, ROBERT C., JR. Malignant papillary cystadenoma of sweat glands with metastases to regional lymph nodes, 348
- HOWE, CHESTER W., AND WARREN, SHIELDS. Myoblastoma, 319
- HYDE, THEODORE L. Cotton surgical suture material, 407

## I

- IASON, ALFRED H. Congenital eventration at umbilicus, 950

## J

- JIRKA, FRANK J. (See Reynolds and Jirka), 485
- JOYNER, AUSTIN. (See Miscall and Joyner), 419

## K

- KAUFMAN, LOUIS RENE, AND HEIMAN, HELEN I. Case of spontaneous gastrojejunal fistula eight years after operative gastrojejunostomy, 557
- KEETON, ROBERT W. Heart and circulation in patients with hyperthyroidism, 657
- KENNEY, FRANCIS R. (See Clute, Kenney, and Hamilton), 739
- KENNEY, WILLIAM E. Prognosis in acute hematogenous osteomyelitis with and without chemotherapy, 477
- KENYON, ALLAN T. Adrenal cortical tumors: physiologic considerations, 194
- KOHLSTAEDT, K. G., AND PAGE, IRVINE H. Terminal hemorrhagic shock, 430
- KRUGER, H. E. (See Freed, Kruger, and Prinzmetal), 914

## L

- LADD, WILLIAM E., AND SCOTT, H. WILLIAM, JR. Esophageal duplications of mediastinal cysts of enteric origin, 815
- LAHEY, FRANK H. Technique of thyroidectomy, 705
- LARGE, ALFRED. Effect of position on shock produced by hemorrhage, 399
- LEHMAN, EDWIN P. (See Burger and Lehman), 542
- LERMAN, JACOB. Endocrine activity of thyroid tumors and influence of thyroid hormone on tumors in general, 266
- LILLY, GEORGE D. Report of 1944 meeting of section on surgery, general and abdominal, of American medical association, 617

## M

- MACBRYDE, CYRIL M. Parathyroid tetany, 804
- MAHORNER, HOWARD. Goiter in southern states, 764
- MCCARTHY, ALPHONSUS M. (See Gore and McCarthy), 865
- MISCALL, LAURENCE, AND JOYNER, AUSTIN. Hemostatic globulin and plasma clot dressings in local treatment of burns, 419
- MONAHAN, DAVID T. Ligation of aorta and both common iliacs for aneurysm, 519
- MOORE, ROBERT A. Benign hypertrophy and carcinoma of prostate, 152

## N

- NACLERIO, EMIL A. (*See* Ficarra and Naclerio), 529  
 NATHANSON, IRA T. Relationship of hormones to diseases of breast, 108  
 NICHOLS, SABRA. (*See* Brunschwig and Nichols), 923  
 NOVAK, EMIL. Ovarian tumors with sex hormone function, 82

## P

- PACK, GEORGE T. (*See* Twombly and Pack), 1  
 PAGE, IRVINE H. (*See* Kohlstaedt and Page), 430  
 PARKHILL, EDITH M. (*See* Broders and Parkhill), 633  
 PEMBERTON, JOHN DEJ., AND BLACK, B. MARDEN. Goiter in children, 756  
 POTH, EDGAR J. (*See* Sarnoff and Poth), 927  
 —, AND ROSS, CHARLES A. Application of succinylsulfathiazole and phthalysulfathiazole to granulation tissue; absorption and excretion, 932  
 PRINZMETAL, MYRON. (*See* Freed, Kruger, and Prinzmetal), 914  
 —, BERGMAN, H. C., AND HECHTER, OSCAR. Demonstration of two types of burn shock, 906  
 PUDENZ, ROBERT H. (*See* Shelden and Pudenz), 884

## R

- REA, CHARLES E. New plan in operative treatment of patients with severe hyperthyroidism, 731  
 REYNOLDS, JOHN T., AND JIRKA, FRANK J. Embolic occlusion of major arteries, 485  
 ROSS, CHARLES A. (*See* Poth and Ross), 932

## S

- SANDUSKY, WILLIAM R. (*See* Cutler and Sandusky), 937  
 SARNOFF, STANLEY J., AND POTH, EDGAR J. Intestinal obstruction; I. Protective action of succinylsulfathiazole following simple venous occlusion, 927  
 SCHIMMEL, IRWIN. (*See* Guthrie and Schimmel), 725  
 SCOTT, CHARLES M. (*See* Woliver and Scott), 947

- SCOTT, H. WILLIAM, JR. (*See* Ladd and Scott, Jr.), 815  
 SELYE, HANS. Experimental investigations concerning role of pituitary in tumorigenesis, 33  
 SHALLOW, THOMAS A., EGER, SHERMAN A., AND CARTY, JAMES B. Primary carcinoma of third portion of duodenum, 939  
 SHANDS, ALFRED R., JR. Analysis of important orthopedic information, 569  
 SHILDEN, C. HUNTER, AND PUDENZ, ROBERT H. Improved retractor for hemilaminectomy, 884  
 SMITHY, H. G. Mixed malignancy of breast, 854  
 SPURLING, ROY G. (*See* Wyatt and Spurling), 561  
 SUGARBAKER, EVERETT D. (*See* Cooper, II, Zumwalt, and Sugarbaker), 886

## T

- TAYLOR, HOWARD C., JR. Endocrine factors in origin of tumors of uterus, 91  
 THOMPSON, WILLARD O. Diagnosis of thyrotoxicosis, 647  
 TWOMBLY, GRAY H. Relationship of hormones to testicular tumors, 181  
 —. (*See* Dean, Woodard, and Twombly), 169  
 —, AND PACK, GEORGE T. Symposium on endocrinology of neoplastic diseases, 1

## W

- WARD, ROBERTSON. Malignant goiter, 783  
 WARREN, SHIELDS. (*See* Howe and Warren), 319  
 Webster, John E. (*See* Gurdjian and Webster), 381  
 Whipple, Allen O. Hyperinsulinism in relation to pancreatic tumors, 289  
 WOLIVER, EDWARD, AND SCOTT, CHARLES M. Spontaneous ventral hernia, 947  
 WOMACK, NATHAN A. Thyroiditis, 770  
 WOODARD, HELEN Q. (*See* Dean, Woodard, and Twombly), 169  
 WYATT, GEORGE M., AND SPURLING, ROY G. Pantopaque, 561

## Z

- ZUMWALT, WILMA. (*See* Cooper, II, Zumwalt, and Sugarbaker), 886



# SUBJECT INDEX\*

Book reviews are indicated by (*B. Rev.*); editorials by (*E.*).

## A

- Absorption and excretion; application of succinylsulfathiazole and phthalylsulfathiazole to granulation tissue (Poth and Ross), 932
- Acute hematogenous osteomyelitis, prognosis in, with and without chemotherapy (Kenney), 477
  - physiologic responses in experimental head injury with special reference to mechanism of death soon after trauma (Gurdjian and Webster), 381
- Adenomatous and diffuse goiter and goiter induced by various agents (Broders and Parkhill), 633
- Adrenal cortical tumors; physiologic considerations (Kenyon), 194
  - hormonal tumors of (Cahill), 233
- Agents, various, goiter induced by, diffuse and adenomatous goiter (Broders and Parkhill), 633
- American association for thoracic surgery, twenty-fifth meeting of (Fishback), 620
  - of genitourinary surgeons, meeting of (Creedy), 466
- broncho-esophagological association, twenty-sixth annual meeting of (Holinger), 470
- college of surgeons cancels 1944 clinical congress, to aid war effort, 629
  - expands graduate training program, 959
- medical association, report of 1944 meeting of section on surgery, general and abdominal (Lilly), 617
- Anesthesia, continuous spinal and general ether, limited comparison of (Cooper et al.), 886
  - in thyroid surgery (Adams and Dixon), 700
  - spinal, as adjunct to preoperative care of patients with severe hyperthyroidism (Rea), 731
  - cystometry after (Bellis), 896
- Aneurysm, ligation of aorta and both common iliaes for (Monahan), 519

- Animals, experimental, receiving steroid hormones, tumors in (Gardner), 8
- Aorta and both common iliaes, ligation of, for aneurysm (Monahan), 519
- Aortography, translumbar; apparatus for injecting radiopaque media (Doss), 422
- Arterial aneurysms, intracranial, 315 (*B. Rev.*)
- Arteries, major, embolic occlusion of (Reynolds and Jirka), 485

## B

- Bacteria in shock due to crushed muscle in dogs (Freed et al.), 914
- Benign hypertrophy and carcinoma of prostate (Moore), 152
- Boeck's sarcoid (Gore and McCarthy), 865
- Book reviews, 168, 315, 475, 632
- Books received, 475, 961
- Breast cancer, effect of sex hormones on skeletal metastases from (Farrow), 141
  - diseases of, relationship of hormones to (Nathanson), 108
  - mixed malignancy of (Smithy), 854
  - primary lymphosarcoma of (Adair), 836
- Broncho-esophagological association, American, twenty-sixth annual meeting of (Holinger), 470
- Burn, severe, physiochemical disturbance in (Ficarra and Naclerio), 529
  - shock, demonstration of two types of (Prinzmetal et al.), 906
- Burns, local treatment of, hemostatic globulin and plasma clot dressings in (Miscall and Joyner), 419

## C

- Cancer, breast, effect of sex hormones on skeletal metastases from (Farrow), 141
- Cancers of prostate gland, endocrine treatment of (Dean et al.), 169
- Carcinoma and benign hypertrophy of prostate (Moore), 152

\*July, pp. 1-168; August, pp. 169-318; September, pp. 319-476; October, pp. 477-632; November, pp. 633-814; December, pp. 815-972.

- Carcinoma—Cont'd  
     primary, of third portion of duodenum (Shallow et al.), 939
- Chemotherapy in hyperthyroidism (Astwood), 679  
     prognosis in acute hematogenous osteomyelitis with and without (Kenney), 477
- Children, goiter in (Pemberton and Black), 756
- Circulation and heart in patients with hyperthyroidism (Keeton), 657
- Circulatory dynamics, recognition, and treatment; terminal hemorrhagic shock (Kohlstaedt and Page), 430
- Colitis, modern management of, 168 (*B. Rev.*)
- Common iliacs, both, and aorta, ligation of, for aneurysm (Monahan), 519
- Complications, management of postoperative, in thyroid surgery (Clute et al.), 739
- Compound craniocerebral injuries (German et al.), 874
- Congenital eventration at umbilicus (Iason), 950
- Cortical tumors, adrenal; physiologic considerations (Kenyon), 194
- Cotton, spool, as suture material (Floyd and Brockbank), 403  
     surgical suture material (Hyde), 407
- Craniocerebral injuries, compound (German et al.), 874
- Crisis, thyroid, problem of (Buxton), 748
- Crushed muscle in dogs, role of bacteria in shock due to (Freed et al.), 914
- Cystadenoma, malignant papillary, of sweat glands with metastases to regional lymph nodes (Horn, Jr.), 348
- Cystometry after spinal anesthesia (Bellis), 896
- Cysts, mediastinal, and esophageal duplications of enteric origin (Ladd and Scott, Jr.), 815
- D**
- Diagnosis of thyrotoxicosis (Thompson), 647
- Diffuse and adenomatous goiter and goiter induced by various agents (Broders and Parkhill), 633
- Diseases, neoplastic, symposium on endocrinology of (Twombly and Pack), 1  
     of breast, relationship of hormones to (Nathanson), 108
- Dissector, sharp, for meniscectomy (Buirge), 956
- Drainage in thyroidectomy (Guthrie and Schimmel), 725
- Dressings, plasma clot, and hemostatic globulin in local treatment of burns (Miscall and Joyner), 419
- Duodenum, third portion, primary carcinoma of (Shallow et al.), 939
- E**
- Editorials, 425, 567, 811
- Embolie occlusion of major arteries (Reynolds and Jirka), 485
- Endocrine activity of thyroid tumors and influence of thyroid hormone on tumors in general (Lerman), 266  
     aspect of enlargements of parathyroid glands (Cope), 273  
     effects of pituitary tumors (German), 47  
     factors in origin of tumors of uterus (Taylor, Jr.), 91  
     treatment of cancers of prostate gland (Dean et al.), 169
- Endocrinologic aspects of tumors of pineal gland (Davidoff), 306
- Endocrinology of neoplastic diseases, symposium on (Twombly and Pack), 1
- Enlargements of parathyroid glands, endocrine aspect of (Cope), 273
- Enteric origin, esophageal duplications of mediastinal cysts of (Ladd and Scott, Jr.), 815
- Esophageal duplications of mediastinal cysts of enteric origin (Ladd and Scott, Jr.), 815
- Estrogen; tumors in experimental animals (Gardner), 10
- Ether, general, and continuous spinal anesthesia, limited comparison of (Cooper, II, et al.), 886
- Eventration, congenital, at umbilicus (Iason), 950
- Excretion and absorption; application of succinylsulfathiazole and phthalylsulfathiazole to granulation tissue (Poth and Ross), 932
- Experimental observations on human ileocecal valve (Buirge), 356
- F**
- Fecal fistula, early recognition of, urobilinogen test as additional aid in (Baronofsky), 377
- Fistula, fecal, early recognition of, urobilinogen test as additional aid in (Baronofsky), 377

## Fistula—Cont'd

- spontaneous gastrojejunal, case of, eight years after operative gastrojejunostomy (Kaufman and Heman), 557
- Fracture orthopedic conferences of Army Air Forces, twelfth regional; analysis of important orthopedic information (Shands, Jr.), 569

## G

- Gall bladder, papilloma of (Greenwald), 370
- Gastrojejunal fistula, spontaneous, case of, eight years after operative gastrojejunostomy (Kaufman and Heman), 557
- Gastrojejunostomy, operative, case of spontaneous gastrojejunal fistula eight years after (Kaufman and Heman), 557
- Gelatin, intravenously infused, retention of (Brunschwig and Nichols), 923
- General ether and continuous spinal anesthesia, limited comparison of (Cooper, II, et al.), 886
- Genitourinary surgeons, meeting of American association of (Creevy), 466
- Gland, cancer of prostate, endocrine treatment of (Dean et al.), 169
- pineal, endocrinologic aspects of tumors of (Davidoff), 306
- Glands, parathyroid, endocrine aspect of enlargements of (Cope), 273
- Globulin, hemostatic, and plasma clot dressings in local treatment of burns (Miscall and Joyner), 419
- Gonorrhea in children (Pemberton and Black), 756
- in southern states (Mahorner), 764
- malignant (Ward), 783
- operability and mortality rate in, factors influencing (Cole), 688
- progress and future in treatment of (Cole), 811 (E)
- Graduate training program, American college of surgeons expands, 959
- Granulation tissue, application of succinylsulfathiazole and phthalylsulfathiazole to; absorption and excretion (Poth and Ross), 932

## H

- Head injury, experimental, acute physiologic responses in, with special reference to mechanism of death soon after trauma (Gurdjian and Webster), 381

- Heart and circulation in patients with hyperthyroidism (Keeton), 657
- Hemilaminectomy, improved retractor for (Shelden and Pudenz), 884
- Hemorrhage, shock produced by, effect of position on (Large), 399
- Hemorrhagic shock, terminal (Kohlstaedt and Page), 430
- Hemostatic globulin and plasma clot dressings in local treatment of burns (Miscall and Joyner), 419
- Hernia, spontaneous ventral (Woliver and Scott), 947
- Hormonal tumors of adrenal (Cahill), 233
- Hormone function, sex, ovarian tumors with (Novak), 82
- thyroid, influence of, on tumors in general, and endocrine activity of thyroid tumors (Lerman), 266
- Hormones, relationship of, to diseases of breast (Nathanson), 108
- to testicular tumors (Twombly), 181
- sex, effect of, on skeletal metastases from breast cancer (Farrow), 141
- steroid, experimental animals receiving, tumors in (Gardner), 8
- Hyperinsulinism in relation to pancreatic tumors (Whipple), 289
- Hyperthyroidism, chemotherapy in (Astwood), 679
- heart and circulation in patients with (Keeton), 657
- severe, new plan in operative treatment of patients with (Rea), 731
- Hypertrophy, benign, and carcinoma of prostate (Moore), 152

## I

- Ileocecal valve, human, experimental observations on (Buirge), 356
- Iliacs, both common, and aorta, ligation of, for aneurysm (Monaahan), 519
- Industrial ophthalmology, 475 (*B. Rev.*)
- Injuries, compound craniocerebral (German et al.), 874
- Injury, experimental head, acute physiologic responses in, with special reference to mechanism of death soon after trauma (Gurdjian and Webster), 381
- Internist, obligations of, to general surgeon (Findley), 567 (E)
- Intestinal obstruction; I Protective action of succinylsulfathiazole following simple venous occlusion (Sarnoff and Poth), 927

Intracranial arterial aneurysms, 315 (*B. Rev.*)

Intravenously infused gelatin, retention of (Brunschwig and Nichols), 923

## K

Kenny method, story of, 425 (*E*)

## L

Leontiasis ossea complicated by Marjolin's ulcer (Burger and Lehman), 542

Ligation of aorta and both common iliacs for aneurysm (Monahan), 519

Local administration of penicillin, method for (Cutler and Sandusky), 937

Lymph nodes, regional, malignant papillary cystadenoma of sweat glands with metastases to (Horn, Jr.), 348

Lymphosarcoma, primary, of breast (Adair), 836

## M

Malignancy, mixed, of breast (Smithy), 854

Malignant goiter (Ward), 783  
papillary cystadenoma of sweat glands with metastases to regional lymph nodes (Horn, Jr.), 348

Management, medical, of thyrotoxicosis (Barr), 668

Marjolin's ulcer, leontiasis ossea complicated by (Burger and Lehman), 542

Mediastinal cysts or esophageal duplications of enteric origin (Ladd and Scott, Jr.), 815

Medical management of thyrotoxicosis (Barr), 668  
physics, 315 (*B. Rev.*)

Meetings, recent, review of, 466, 470, 617, 620

Meniscectomy, sharp dissector for (Buirge), 956

Metastases, skeletal, from breast cancer, effect of sex hormones on (Farrow), 141

Military surgeons of United States, association of, 630

Mortality rate and operability in goiter, factors influencing (Cole), 688

Muscle, crushed, in dogs, role of bacteria in shock due to (Freed et al.), 914

Myelography, notes on absorption following; pantopaque (Wyatt and Spurling), 561

Myoblastoma (Howe and Warren), 319

## N

Neoplastic diseases, symposium on endocrinology of (Twombly and Pack), 1

Notices, 629-631, 959

## O

Obliterations of internist to general surgeon (Findley), 567 (*E*)

Obstruction, intestinal; I. Protective action of succinylsulfathiazole following simple venous occlusion (Sarnoff and Poth), 927

Occlusion, embolic, of major arteries (Reynolds and Jirka), 485

of external pancreatic secretion, survival of rhesus monkey four years after excision of head of pancreas with (Brunschwig), 416

simple venous, protective action of succinylsulfathiazole following; intestinal obstruction (Sarnoff and Poth), 927

Operability and mortality rate in goiter, factors influencing (Cole), 688

Operative treatment of patients with severe hyperthyroidism, new plan in (Rea), 731

Ophthalmology, industrial, 475 (*B. Rev.*)

Orthopedic information, important, analysis of (Shands, Jr.), 569

Osteomyelitis, acute hematogenous, prognosis in, with and without chemotherapy (Kenney), 477

Ovarian tumors with sex hormone function (Novak), 82

## P

Pain mechanisms, 317 (*B. Rev.*)

Pancreas, excision of head of, with occlusion of external pancreatic secretion, survival of rhesus monkey four years after (Brunschwig), 416

Pancreatic tumors, hyperinsulinism in relation to (Whipple), 289

Pantopaque (Wyatt and Spurling), 561

Papillary cystadenoma, malignant, of sweat glands with metastases to regional lymph nodes (Horn, Jr.), 348

Papilloma of gall bladder (Greenwald), 370

Parathyroid glands, endocrine aspect of enlargements of (Cope), 273  
tetany (MacBryde), 804

Penicillin, method for local administration of (Cutler and Sandusky), 937

- Phthalysulfathiazole and succinylsulfathiazole, application of, to granulation tissue; absorption and excretion (Poth and Ross), 932
- Physical foundations of radiology, 632 (*B. Rev.*)
- Physies, medical, 315 (*B. Rev.*)
- Physiochemical disturbance in severe burn (Ficarra and Naclerio), 529
- Physiologic considerations; adrenal cortical tumors (Kenyon), 194  
responses, acute, in experimental head injury with special reference to mechanism of death soon after trauma (Gurdjian and Webster), 381
- Pineal gland, endocrinologic aspects of tumors of (Davidoff), 306
- Pituitary in tumorigenesis, experimental investigations concerning role of (Selye), 33  
tumors, endocrine effects of (German), 47
- Plasma clot dressings and hemostatic globulin in local treatment of burns (Miscall and Joyner), 419
- Position, effect of, on shock produced by hemorrhage (Large), 399
- Postoperative complications, management of, in thyroid surgery (Clute et al.), 739
- Primary carcinoma of third portion of duodenum (Shallow et al.), 939  
lymphosarcoma of breast (Adair), 836
- Problem of thyroid crisis (Buxton), 738
- Prognosis in acute hematogenous osteomyelitis with and without chemotherapy (Kenney), 477
- Progress and future in treatment of goiter (Cole), 811 (*E*)
- Prostate, carcinoma and benign hypertrophy of (Moore), 152  
gland, cancers of, endocrine treatment of (Dean et al.), 169
- R
- Radiology, physical foundations of, 632 (*B. Rev.*)
- Radiopaque media, apparatus for injecting; translumbar aortography (Doss), 422
- Rate, mortality, and operability in goiter, factors influencing (Cole), 688
- Rehabilitation of war injured, 316 (*B. Rev.*)
- Responses, acute physiologic, in experimental head injury with special reference to mechanism of death soon after trauma (Gurdjian and Webster), 381
- Retention of intravenously infused gelatin (Brunschwig and Nichols), 923
- Retractor, improved, for hemilaminectomy (Shelden and Pudenz), 884
- Rhesus monkey, survival of, four years after excision of head of pancreas with occlusion of external pancreatic secretion (Brunschwig), 416
- S
- Sarcoid, Boeck's (Gore and McCarthy), 865
- Secretion, external pancreatic, survival of rhesus monkey four years after excision of head of pancreas with occlusion of (Brunschwig), 416
- Severe burn, physiochemical disturbance in (Ficarra and Naclerio), 529
- Sex hormone function, ovarian tumors with (Novak), 82  
hormones, effect of, on skeletal metastases from breast cancer (Farrow), 141
- Shock, burn, demonstration of two types of (Prinzmetal et al.), 906  
due to crushed muscle in dogs, role of bacteria (Freed et al.), 914  
produced by hemorrhage, effect of position on (Large), 399  
terminal hemorrhagic (Kohlstaedt and Page), 430
- Southern states, goiter in (Mahorner), 764
- Spinal anesthesia, cystometry after (Bellis), 896  
use of, as adjunct to preoperative care of patients with severe hyperthyroidism (Rea), 731  
continuous, and general ether anesthesia, limited comparison of (Cooper, II, et al.), 886
- Spontaneous gastrojejunal fistula, eight years after operative gastrojejunostomy, case of (Kaufman and Heiman), 557  
ventral hernia (Woliver and Scott), 947
- Spool cotton as suture material (Floyd and Brockbank), 403
- Steroid hormones, experimental animals receiving, tumors in (Gardner), 8

- Stomach, report of case involving;  
Boeck's sarcoid (Gore and Mc-  
Carthy), 865
- Story of Kenny method, 425 (E)
- Succinylsulfathiazole and phthalysulfathiazole, application of, to granulation tissue; absorption and excretion (Poth and Ross), 932
- following simple venous occlusion; intestinal obstruction (Sarnoff and Poth), 927
- Sulfamerazine; role of bacteria in shock due to crushed muscle in dogs (Freed et al.), 914
- Sulfasuxidine and sulfathalidine; application of succinylsulfathiazole and phthalysulfathiazole to granulation tissue; absorption and excretion (Poth and Ross), 932
- Sulfathalidine and sulfasuxidine; application of succinylsulfathiazole and phthalysulfathiazole to granulation tissue; absorption and excretion (Poth and Ross), 932
- Surgeon, general, obligations of internist to (Findley), 567 (E)
- Surgery, general and abdominal, of American medical association, report of 1944 meeting of section on (Lilly), 617
- year book of, 316 (B. Rev.)
- thyroid, anesthesia in (Adams and Dixon), 700
- management of postoperative complications in (Clute et al.), 739
- Surgical suture material, cotton (Hyde), 407
- Suture material, cotton surgical (Hyde), 407
- spool cotton as (Floyd and Brockbank), 403
- Sweat glands, malignant papillary cystadenoma of, with metastases to regional lymph nodes (Horn, Jr.), 348
- Symposium, endocrinology of neoplastic diseases, 1-314
- on surgical lesions of thyroid, 633-814
- T
- Technique of thyroidectomy (Lahey), 705
- Terminal hemorrhagic shock (Kohlstaedt and Page), 430
- Test, urobilinogen, as additional aid in early recognition of fecal fistula (Baronofsky), 377
- Testicular tumors, relationship of hormones to (Twombly), 181
- Tetany, parathyroid (MacBryde), 804
- Thoracic surgery, twenty-fifth meeting of American association for (Fishback), 620
- Thyroid crisis, problem of (Buxton), 748
- hormone, influence of, on tumors in general, and endocrine activity of thyroid tumors (Lerman), 266
- surgery, anesthesia in (Adams and Dixon), 700
- management of postoperative complications in (Clute et al.), 739
- surgical lesions of, symposium on, 633
- tumors, endocrine activity of, and influence of thyroid hormone on tumors in general (Lerman), 266
- Thyroidectomy, drainage in (Guthrie and Schimmel), 725
- technique of (Lahey), 705
- Thyroiditis (Womack), 770
- Thyrotoxicosis, diagnosis of (Thompson), 647
- medical management of (Barr), 668
- Translumbar aortography; apparatus for injecting radiopaque media (Doss), 422
- Trauma, mechanism of death after, acute physiologic responses in experimental head injury with special reference to (Gurdjian and Webster), 381
- Treatment, endocrine, of cancers of prostate gland (Dean et al.), 169
- operative, of patients with severe hyperthyroidism, new plan in (Rea), 731
- Tumorigenesis, pituitary in, experimental investigations concerning role of (Selye), 33
- Tumors, adrenal cortical; physiologic considerations (Kenyon), 194
- hormonal, of adrenal (Cahill), 233
- in experimental animals receiving steroid hormones (Gardner), 8
- of pineal gland, endocrinologic aspects of (Davidoff), 306
- of uterus, endocrine factors in origin of (Taylor, Jr.), 91
- ovarian, with sex hormone function (Novak), 82
- pancreatic hyperinsulinism in relation to (Whipple), 289
- pituitary, endocrine effects of (German), 47
- testicular, relationship of hormones to (Twombly), 181
- thyroid, endocrine activity of, and influence of thyroid hormone on tumors in general (Lerman), 266
- Twenty-sixth annual meeting of American broncho-esophagological association (Holinger), 470

## U

- Ulcer, Marjolin's leontiasis ossea complicated by (Burger and Lehman), 542
- Umbilicus, congenital eventration at (Iason), 950
- Urobilinogen test as additional aid in early recognition of fecal fistula (Baronofsky), 377
- Urology award, 959
- Uterus, tumors of, endocrine factors in origin of (Taylor, Jr.), 91

## V

- Valve, human ileocecal, experimental observations on (Buirge), 356
- Ventral hernia, spontaneous (Woliver and Scott), 947

## W

- War injured, rehabilitation of, 316 (*B. Rev.*)

## Y

- Year book of general surgery, 316 (*B. Rev.*)

